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NUMBER 6
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1. Hollister, L. E., Krieger, G. E., Kringel, A., and Roberts, R. H.: Ann. New York Acad. Sc. *61*:92 (April 15) 1955. 2. Hoffman, J. L., and Konchegul, L.: Ann. New York Acad. Sc. *61*:144 (April 15) 1955. 3. Kline, N. S., and Stanley, A. M.: Ann. New York Acad. Sc. *61*:85 (April 15) 1955.

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2. Thompson, L., Procter R., *North Carolina M. J.*, 15:596, 1954

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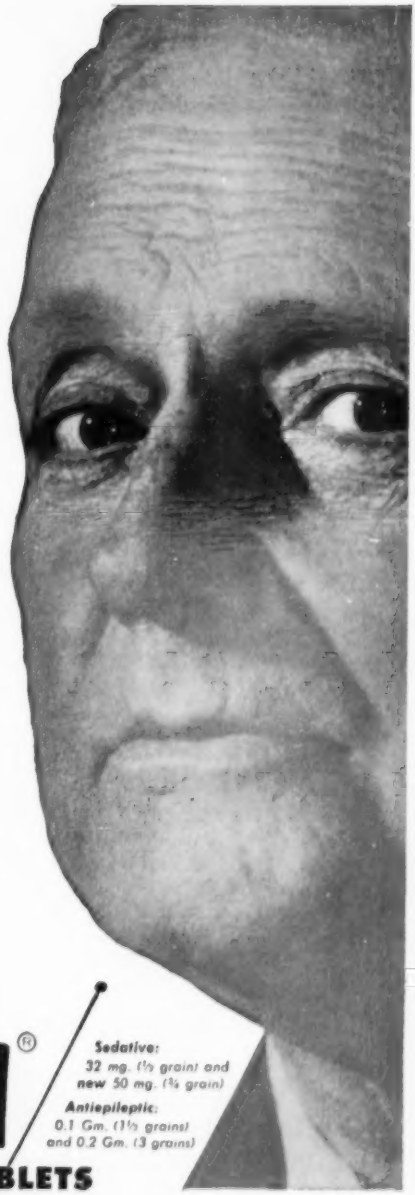

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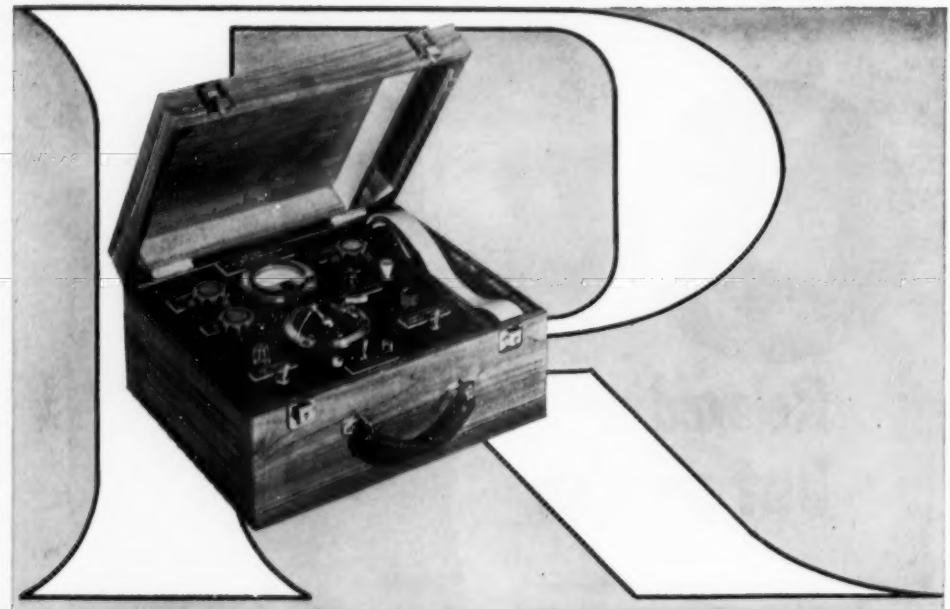

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1. Overholser, W.: in Chlorpromazine and Mental Health, Philadelphia, Lea & Febiger, 1955.
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GENETIC PRINCIPLES IN HUMAN POPULATIONS [1, 2]

H. J. MULLER, D. Sc., Bloomington, Ind.

The heredity-environment controversy, which had already been raging for a long time in this writer's student days a half-century ago, is an excellent example of wishful thinking by 2 sets of fanatical opponents, both of whom ought to know better.

HEREDITY AND ENVIRONMENT

It is of course absurd to deny the influence of environment in giving rise to alterations in living things. Its importance is illustrated by the fact that life is sometimes defined as a continual adjustment of inner to outer conditions. Although this definition misses the main point, such adjustment is certainly characteristic of living things. Moreover, the higher they are the more applicable is the statement. Thus, the most advanced system in the most advanced organism, namely, the central nervous system in man, has this kind of adjustment as its primary function. In consequence, it achieves a degree of plasticity of response far exceeding that of anything else we know. We must admit that in this sense its reactions are determined in great detail by its surroundings. And yet we also know that the human organization, including that of its nervous system, is a superlatively intricate one, more intricate than any other known structure. Thus its capacity to carry out these varied reactions, and the exact form taken by them, depend not only on its past and present environment but also on what complexities of inner constitution have been provided by its long prior course of evolution and by its more immediate circumstances of ancestry.

It follows that nongenetic conditions, for their part, can determine such enormous differences in response as those between the civilized man and the savage, and those between the normal man and the victim of polio, of oxygen deprivation at birth, or of a sadistic foster father. On the other hand heredity, for its part, can predetermine such differences as those between a man and a fish, and those between a normal man and a sufferer from anencephaly, phenylpyruvic amentia, or Huntington's chorea. Moreover, even abnormalities which appear to the superficial observer to be of exactly the same kind, such as a grossly underweight condition in two different persons, or a strikingly deformed cranium, or an apathetic disposition, may in one case be traced to imposed conditions of living and in another case to peculiarities of the biological inheritance.

Today, although few people would deny that differences as gross as those just mentioned can be caused by either environment or heredity, opinion tends to fall into two camps with regard to the causation of the smaller differences, especially those within the range vaguely delimited as "normal." Yet we all know that, so far as environmental effects are concerned, the lesser deviations from the mean are more numerous than the more extreme ones, and that the effects tend in general to follow a normal curve of frequency distribution. Similarly, studies in heredity have shown that, when any measurable characteristic is considered, the mutations causing smaller deviations (many of them quite invisible) arise more frequently than the so-called large mutations. Moreover, the larger the effect of the mutation the more harmful is it likely to be and the smaller, in consequence, will be the number of descendants to whom it will be passed down. For these two reasons the hereditary effects, like the environmental ones, will tend to give rise to a more-or-less normal curve, in the case of most quantitatively varying traits. The observed curve will of course be a resultant of both the environmental and genetic variations acting together, in a more or less cumulative although far from strictly additive manner.

What proportion of the differences de-

[1] Read in abbreviated form in the symposium on "Recent Progress in Genetics and its Implications for Psychiatric Theory" at the 112th annual meeting of The American Psychiatric Association, Chicago, Ill., April 30-May 4, 1956.

[2] From the Department of Zoology, Indiana University (Contribution No. 614).

pends upon hereditary rather than environmental causes is a matter that varies widely according to the trait under consideration, the genetic nature of the population, and the existing environmental complex. For example, the skin color variations seen in Harlem, New York City, are mainly genetic while those seen on the beach at, say, Brighton, England, are mainly caused by differences in exposure to sunlight. Each problem, then, requires separate assessment, based on empirical evidence. The task is especially difficult when, as in the case of mental traits, given types of cultural and material environments that may influence the result tend to be handed down in families, thus confusing the estimate of what is contributed by biological inheritance.

This is not the place to describe the method of attack on this difficulty provided by a comparison of the differences shown by identical twins, fraternal twins, ordinary sibs, and unrelated individuals of the same population, respectively, and also by data on sibs reared apart or differently and on unrelated as compared with related persons reared together. Suffice it to say that, despite the cogent criticisms raised by Price(1), by Neel and Schull(2), and others against certain of the simplifying assumptions of the twin studies, the results for mental traits are in reasonably good accord with those otherwise arrived at, as for instance by the studies on foster children. Thus, for those features of intelligence measured by Binet tests, it may be concluded that in middle-class American communities the hereditary contribution to the variance is commonly about double that of the environment.

In this connection it is to be observed that the tendency of one fetus to gain an advantage over the other is usually stronger for identical than fraternal twins, because of their closer association and greater tendency to mirror-imaging. Hence this factor, which appears to be the most important one interfering with a simple interpretation of comparisons between identical and fraternal twin differences, acts to decrease the resemblances between identical twins more than those between fraternal twins. It thereby leads to an underrating rather than an exaggeration of the influence of heredity, as gauged by the twin method. On the other hand, the main influence which seems to act in the opposite direction, the greater tendency of identical twins, because of their greater likeness, to be treated more nearly alike and to adopt more similar environments, does not entirely constitute a methodological fault. For heredity always acts, in part, by influencing the selection, and in fact the creation, of the environment of the given individual. That is, this ecological channel is an admitted and important path of action of some hereditary differences, in non-twins as well as in twins, and the results of this type of action are not ordinarily to be separated from those of the more direct operations of the hereditary mechanism.

It is important to realize that, however great the influence of environment may be upon the structure and functioning of the organism, the modifications thereby arising do not result in corresponding changes in the hereditary material. They therefore fail to be transmitted germinally. It would take us too far afield to demonstrate here that the archaic folk belief in the inheritance of acquired characters, which goes by the name of Lamarck since he espoused it as the method of evolution, is entirely irreconcilable with the fundamental genetic principles of accurate gene segregation and reduplication, and the fortuitous microdistribution of mutations. Nor can we review the numerous direct tests of this matter. No doubt it was largely the false promise of easy progress offered by the Lamarckian doctrine that led to its repeated revival by nongeneticists having special pleadings to make in regard to problems of the mind or nervous system, such as Driesch and Semon (who based their belief on a cellular psyche), MacDougal (whose results were discredited by those of Crew in a repetition of the experiments), and Pavlov (who subsequently discovered and admitted that his work had been technically faulty). Later, Stalin the omniscient, using Lysenko as his mouthpiece, made Lamarckism, under the title Michurinism, the basis of all Communist biology. However, in view of the "resignation" of Lysenko, announced only a short time ago, there will probably be a considerable interim before another claimant arises to herald his

discovery of new proof of this doctrine. In the meanwhile, it is high time for all those in fields affected by these matters to adjust their outlook, if they have not already done so, to the modern genetic conceptions of heredity and variation.

HOW THE HEREDITARY CARDS ARE SHUFFLED

According to modern genetics, each of the 24 different chromosomes present in a mature human sperm or egg cell is differentiated along the length of its coiled thread of polymerized nucleic acid into hundreds of functionally distinct regions, denoted by the geneticist as "genes." After union of the egg and sperm nuclei at fertilization there are 2 sets of 24 chromosomes present. We say that these 48 chromosomes constitute 24 pairs because each of the 24 chromosomes from the mother is matched by a homologous or partner chromosome from the father. This partner contains corresponding genes, that are ordinarily arranged in line within it in just the same sequence, with the exception of a portion of the pair of chromosomes that differentiates the sexes. Although the corresponding or *allelic* genes, those that occupy the same position in line in 2 homologous chromosomes, are often of identical composition, there are always some genes here and there which are not just like their alleles in the partner chromosome. Partner chromosomes present these differences because they have been derived from different parents and no pair of parents, taken from a heterogeneously breeding population, are of absolutely identical gene content.

Before we consider the past and future history of these gene differences in the population let us review some other essentials of gene and chromosome behavior. The most remarkable faculty of each gene lies in the fact that it constructs a duplicate of itself, an act that forms the basis of all growth and reproduction. That is, the gene collects, next to itself, scattered bits of given raw materials that lie about it in the nuclear fluid, rearranging them and binding them together into a pattern identical with its own. As this happens all along the chain of genes that forms each chromosome the consequence is that in place of each original chromosome there now appears to be 2 of them, as if it had split in half, although the process was really that of multiplication, not division, by 2. Since at the ensuing cell division the 2 members of each of the 48 chromosome doublets are pulled into opposite daughter cells, it follows that each of these cells gets to have a representative of each of the 48 chromosomes that the original cell had had, and of every gene within each of these 48 chromosomes. As this process of precise doubling and apportionment takes place at each of the successive divisions of the fertilized egg and of the body derived from it, all the cells in the body proper may be expected to contain in their nuclei both original sets of chromosomes, 24 in each set, and all their included genes, those derived from both parents. (There is, however, some possibility of certain systematic gene changes associated with the differentiation of somatic cells—a matter as yet uncertain—and, as we shall see, there is always a chance for the occurrence of occasional random mutations during the multiplication of the body cells.)

Now since a person is derived from an egg and a sperm cell each of which contained but 1 set of 24 chromosomes, the 2 sets of chromosomes, 48 in all, present in any person's cells must somehow become reduced to one set of 24 again during the process of maturation of his own germ cells to form eggs or sperm, in preparation for the next act of fertilization. This happens through the physical coming together, or *synapsis*, of all partner or homologous chromosomes, 2 by 2, in parallel arrangement with all corresponding genes apposed, followed by the apposed members being pulled or *segregated* to opposite daughter cells, in a cell division that has not been preceded by chromosome doubling. If in the case of a given pair of partner chromosomes the maternal member, that originally derived from the person's mother, chances to be pulled to a given daughter cell that is to become a sperm, it is purely a matter of chance, with equal probabilities of occurrence, whether the maternal or the paternal member of any other pair will be pulled into that same cell. Thus, although the mature germ cell (sperm or egg) comes to contain just one complete set of chromosomes, that set is not derived in its entirety from either the father or the mother

of that individual (or, as we may say, the grandfather or the grandmother of the prospective offspring), but is a mosaic, or recombinant, derived partly from each.

The mosaicism or recombination is on an even finer scale of subdivision than the account given thus far would indicate, however. This is because, before the partner chromosomes separate, they have engaged in a curious exchange of corresponding pieces, known as crossing over. This involves a breakage of the 2 homologous chromosome threads at one or more exactly corresponding points, and a criss-cross joining together of the pieces. If the fingers of one hand were to represent one set of (only 5) chromosomes, it would be much as though a given finger of one hand had had its end replaced by the corresponding end of that finger of the other hand, and vice versa, in a kind of mutual transplantation process. Sometimes the pieces transferred are longer, sometimes shorter, and sometimes they are sections from the middle instead of the end. In consequence of all this, the complete set of 24 chromosomes present in each germ cell constitute a rather intricate mosaic work, or recombination, of the two sets that had been contributed to the fertilized egg a whole generation previously.

It follows from this series of events that any individual gene is represented only once in the mature germ cell's set, being either the original maternal gene, now to be called grandmaternal, or the corresponding but perhaps somewhat different grandpaternal one. This may be called Mendel's first law. If now a mature germ cell happens to contain a given gene of grandmaternal origin then the chance that it will also contain some other grandmaternal gene, that lies in a different chromosome, rather than the corresponding grandpaternal one, will be just 50%. This is the basis of Mendel's second law. However, if that other grandmaternal gene, instead of lying in a different chromosome, happens to lie in the same chromosome as the first grandmaternal gene under consideration, it will inevitably come to be included in the same mature germ cell with the first one except in those cases in which the pair of chromosomes in question has undergone breakage and crossing over *between* the points at which these genes are located. The chance for just this exchange to occur is usually less than 50%, and it is evident that the nearer together in the chromosome the 2 genes in question are placed, the smaller will be the frequency of cases in which they happen to become separated in this way. The genes are then said to be *linked*, and a study of the frequency of their separation in heredity, carried out by tabulating the characteristics of the offspring, allows an estimate to be made of the relative positions of the genes in question in the chromosome. By this method the so-called chromosome maps have been drawn up. They are no mere speculations. Their physical validity has been verified in a number of ways by direct microscopic observation, even though the genes themselves are too small to be distinguished by the highest power that it is practicable to use.

The biological function of the whole complicated process of sexual reproduction, including fertilization, the operation of Mendel's laws of segregation, and crossing over, that is, the advantage of this system of events to the species, lies in the mosaic genetic patterns it furnishes. In other words, the important thing here is the provision, in successive generations, of individuals having diverse combinations of the genes in regard to which the individuals of earlier generations had differed. For in the testing out of these varied combinations in the trials of life, some prove to be better able than the average to survive and multiply under given conditions, and in the course of many generations those favored combinations will tend, under those conditions, to crowd out the earlier genetic combinations. Thus the population will have evolved.

MUTATIONS AND THEIR CONSEQUENCES

It is evident that the formation of these new combinations is dependent upon the preexistence of differences between the corresponding genes of different individuals. These gene differences have not themselves arisen by the formation of new combinations of genes, however. They come about by sporadic changes of chemical composition, called mutations, that usually occur pointwise, within a single gene at a time, in a single cell at a time. The mutation is in a sense an accident on an ultramicroscopic

scale, involving the collision of a gene with some potent chemical particle, or bolt of radiation. The changed or mutant gene is in the great majority of cases impaired in its functioning, inasmuch as the change was not Lamarckian; that is, it was not the result of an adaptive reaction. For blind changes made in any complicated organization are nearly always harmful. Very rarely, however, the modification of gene functioning will happen by a fortunate accident to be of an advantageous nature; at least it may have an advantageous effect under given circumstances. It is only because of the occurrence of these occasional mutations of a potentially beneficial kind that sexual reproduction, by giving new combinations of these mutant genes, serves to promote evolution. All this implies, of course, that the mutant gene, when it forms its daughter gene, copies its new structure rather than reproducing the old type. It is only because it can do this that the mutant gene can become permanently incorporated in the species.

We must infer that each one of our thousands of present-day genes represents the product of a long succession of advantageous mutations (the far more numerous disadvantageous ones having died out). These advantageous, selected mutations have gradually differentiated each gene, and caused it to become ever more specialized and more nicely adapted to playing its present role or roles, whatever they may be, in the system of operations occurring in the organism. By the selection of the better combinations of those newer mutant genes that at present exist only in scattered individuals in a population the process can be carried further. But after these combinations have become established as the norm of the population further genetic progress must involve the occurrence of still further mutations, which in their turn must be shuffled in the sexual process and subjected to selection.

Before considering further the processes of accumulation and elimination of mutant genes in populations, let us review some facts regarding the relations of the genes to the characteristics of the organism. Whatever may be the nature of the primary chemical products of the genes within the cell, these products must be of thousands of kinds, corresponding with the thousands of different genes, and these products must interact with one another in innumerable ways to form secondary products, tertiary products, and those ever further removed from the genes. It is usually only after a most intricate web of these interactions has been followed through that those end-products are at last found which we become aware of as the characteristics of the organism. For only certain features, mostly of a superficial kind, are open to the view of us shortsighted spectators.

Because of the great indirectness of the route connecting the genes with these end-results that we see, it is evident that any given characteristic must be a resultant of the action of many genes, some playing a major role in its development but many more playing only a minor role. Moreover, since some of the reactions constituting the web that leads from gene to character are likely to be more or less responsive to the influence of given environmental conditions, the degree and kind of development of each trait will depend to some extent upon these extragenic influences also. It follows that the rules of simple Mendelian inheritance, giving for example a clear-cut 3 to 1 or 1 to 1 ratio among offspring, will operate only in the relatively rare cases in which the observed individuals differ in regard to just one pair of genes that has a major influence on the character studied, and in which the environmental effects also are minor in comparison with those of this gene-pair. Thus a gene should not be regarded as the absolute determiner of a trait, but only as a conditional determiner, one that gives rise to the possibility of a given biological effect being produced, provided other conditions, genetic and environmental, are appropriate. The degree of this conditionality itself varies according to both the gene and these conditions. In another sense too a given gene is not the simple determiner of a given trait, inasmuch as the reactions it initiates, by participating in the biochemical web of processes previously referred to, usually produce multiple effects, as a result of the branching of the web. Nevertheless there is often just one major conspicuous effect, a more characteristic symptom, by which, in practice, we identify a given gene's presence.

The prevalent type with regard to any

given trait, that which we call the normal, represents the present-day end-point of a most protracted evolutionary sequence and therefore exhibits that degree of development of the characteristic which in most cases has for a very long time been optimal, even though under present-day conditions it may no longer be optimal. It has accordingly been to the advantage of the species to incorporate within its genetic composition those genes, originally mutant, which aided in the development of the trait that we call normal and which tended to insure its development to approximately its present degree even in the face of fluctuating conditions, and variations in minor genes. It is true that the possibility of considerable latitude in development and in physiological reactions also becomes included in the genetic organization, allowing adaptive responses to certain standard variations in the environment, but we do not here refer to this type of influence on the organism. In consequence, now, of the stabilizing arrangements set up by the prolonged selection for "normality," we find that a trait usually tends to develop to nearly its normal degree even in an individual who has received from just one of his parents a mutant gene that would have produced a marked deviation, if it had been received from both parents. In other words, in the genetically half-normal, half-mutant individual, whom we call a *heterozygote*, the normal gene tends to be *dominant* and its mutant allele to be *recessive*, so that the heterozygous individual usually appears to be much more like the "pure" or homozygous normal type than like the homozygous mutant (the type which receives the mutant gene from both his parents). Nevertheless, even where dominance of the normal at first sight seems complete, searching investigation usually reveals some influence of the mutant gene in the heterozygous individual. That is, the mutant gene does have at least a small degree of dominance in most cases, and in the case of a minority of mutant genes the dominance of the mutant is considerable and conspicuous.

Now, despite the fact that every species has been subjected to so long a process of selection for stabilization of its traits at the so-called "normal" level, it is notorious that most populations display a large amount of variability in practically every respect. That considerable portion of this variation which is genetic is of course the result of the continued occurrence of mutations. However, not everyone who is a genetic variant from the norm in some respect, or from his parents' average, represents a newly arisen mutation—in fact, this is very far from the case. Most of the observable variations represent the diverse products of recombination of a great multitude of mutations, the great majority of them minor in their individual effects. All but a few of these mutations arose in remote ancestors and have been handed down ever since, with perpetual shuffling of their combinations.

OUR LOAD OF HARMFUL GENES

It is possible to make some calculations regarding the number of mutant genes present in a population. As we have seen, the great majority of the mutant genes that arise are detrimental. Now each detrimental mutant gene has only a limited persistence in the population, that is, a limited number of generations during which it will, on the average, be handed down. For at long last its detrimental effect will cause some individual containing it to die before reproducing, or to fail to reproduce, in consequence of the disability caused by that gene. Of course there will also be many cases in which an individual dies off for some reason that has nothing to do with the gene in question, but to balance these there will in any stable population be as many cases of the accidental multiplication of such individuals to a greater extent than the average. Thus the average number of generations through which a mutant gene is transmitted depends upon its own "merits." For instance, if it is disadvantageous enough to give its possessors one chance in 20, or 5%, of dying out, then it will on the average manage to persist through 20 generations—the reciprocal of its 1/20 disadvantage—before it brings extinction to its line. For it is clear that, on the average, a 1/20 chance of death must require 20 repetitions before it hits the mark, somewhat as in "Russian roulette." If, now, a group of mutant genes conferring a 1/20 disadvantage should arise anew by mutation in each generation with a frequency of, say, 1 among

every 100 individuals, it will follow that in any one generation approximately 20 times 1%, that is, 20% of the population, will contain these genes. For the population will contain the total number that can accumulate for the 20 generations of their persistence. In other words, the frequency of any genes must be equal to their frequency of origination by mutation in one generation multiplied by the number of generations that they persist.

The curious fact emerges from such calculations that a type of mutant gene that harms its possessor only a little does an amount of damage to the population comparable with that done by a gene having a drastically injurious effect. For one thing, each slightly harmful gene, on the average, causes the extinction of its line, by finally bringing about the misfortune of premature death or failure to reproduce, if only by acting as the deciding factor at some critical time. Secondly, even though it produces only a slight handicap, the number of individuals whom it affects, that is, its persistence, is the reciprocal of the amount of damage, so that the total damage it does is about as great as for the very harmful gene. Finally, this damaging effect of the so-called small mutations actually applies to every individual in the population. For, as we shall see, the small mutations attain such a high frequency, by accumulation, that every individual carries some of them and is somewhat reduced in "fitness" by them. Because of the reciprocal relation between accumulation and degree of damage already mentioned, the amount of this effect exerted on an individual by a group of genes of a given mutation frequency will on the average be proportional to that mutation frequency, regardless of the amount of damage done by the separate mutations. That is, genes of more frequent origin will do proportionately more damage, no matter how little or how much harm any one such gene does to one individual. Of course this principle applies to mental just as well as to other features.

We are on much less certain ground when we turn from these principles to a quantitative estimation of the frequency with which mutations arise in man, the amount of their accumulation, and the degree of reduction of fitness of the individual or population that they occasion. However, there are a number of ways of obtaining evidence regarding these matters, and it happens that they all point toward approximately the same conclusions. One way of estimating the total frequency with which mutations arise per generation is to take the average figure for mutation frequency of an individual gene and then multiply it by the probable number of genes. There are several large sources of error in connection with both these figures, but according to a provisional estimate which I have made in this way at least 1 person in every 5, on the average, and possibly 2, 3, or even 4 in 5, are carriers of detrimental mutant genes that their parents did not have; that is, there is this frequency of genes representing newly arisen mutations.

This, even at the lowest value that I regard as probable, is a startling figure. For it must be borne in mind that, in effect, every mutant gene that arises must finally be eliminated by extinction of an individual carrying it, and that therefore, over a long course of generations, there must be as many extinctions per generation as newly arisen mutations if the population is not to deteriorate by accumulating ever more of them. Of course some individuals, having a considerable excess of mutant genes over the average number in the population, can in dying account for the elimination of 2 or more of these genes at once, but on the whole the number of individuals dying out genetically must be of the same order of magnitude as the number of new mutations. It is unlikely that the frequency of dying out is as great as this at present, however. For fewer than a fifth of persons now born in our country fail to grow up and reproduce, and many of those who do fail represent misfortunes of environment rather than of heredity. Thus it seems likely that under modern civilization mutant genes are arising in our population a good deal faster than they are being eliminated—that is, they are accumulating.

Through how many generations does the crop of mutations of each generation ordinarily tend to persist, and thus to form an accumulated load of mutations carried by each individual? Light on this question is thrown by the findings that show that even seemingly recessive mutations usually have some small amount of dominance, at least.

For this dominance, by allowing the mutant gene to harm even the heterozygous individual to some extent, results in a much lower persistence than if the gene, before it could do any harm, had to wait for many generations until by mischance it met one like itself at fertilization and thus became homozygous. Even with its slight dominance, however, it is probable that the average detrimental mutant gene persists for several scores of generations, although this is seldom enough to allow it to become homozygous. Multiplying this persistence estimate of several scores of generations by our rather inexact estimate of the frequency of new mutations we see that all of us must be carrying something of the order of a dozen to several dozen of these detrimental genes. All taken together, they must lower our fitness considerably.

Light on this problem is thrown from another angle by examination of the results of inbreeding, as in first cousin marriages, for this practice gives a calculable chance of formation of individuals homozygous for any detrimental genes that are present, and there is a consequent measurable increase in the frequency of premature deaths as well as of other expressions of lowered fitness. The results of such studies are in harmony with those of the preceding line of investigation. They indicate that everyone carries a collection of detrimental genes so large that only a fourth, or even fewer, of these genes would have been sufficient to kill or sterilize him, under the given conditions of living, if these genes had been in homozygous instead of heterozygous condition(3). Estimating their amount of dominance as averaging about 5%, this would result in a lowering of the expectation of life and reproduction of the average heterozygous individual by about 20%, as compared with an "ideal" man not harboring any such mutant genes heterozygously.

SALUTARY DIVERSITY

The definitely detrimental genes that we have been considering are by no means the only basis of the genetic variation existing in a population. The great majority of measurable traits have a certain range of variation within which a difference in a given direction has little if any consistent or over-all influence on the individual's chances of survival or reproduction, in that a given difference, such as for instance a somewhat greater height, may according to variable circumstances and accompanying genes be as likely to be advantageous as disadvantageous. Thus, although a given difference is hardly ever effectively neutral in selective value when the rest of the genes are held constant, nevertheless the different alleles of different genes are likely to have become balanced at a series of frequencies such as to result in the average value of the trait being as near as possible to the optimum in relation to any long-standing conditions of living.

In addition, the range of variation is sometimes kept wide by an active process of natural selection. This happens in cases in which a given minority type finds itself at a premium when its numbers are below a certain level but is at a disadvantage when numerous. This sort of thing has a geographic basis if a portion of the territory of a fairly stationary population presents special environmental conditions, favoring the type in question, that are not found in the territory at large. It has a more purely ecological basis where, within the same territory, there are advantages to the species in having diverse capabilities and attributes, specialized for different modes of life, but the result will not follow unless mechanisms exist for allocating the individuals into those ecological niches for which they are better adapted. Such mechanisms often occur among animals of comparatively high intelligence, especially human beings. It has long been a pet contention of mine, for example, and it is one that has been independently espoused by the distinguished ophthalmologist Dr. Riddell of Glasgow, that myopia, although certainly a detrimental condition for most individuals, was advantageous in primitive communities for those possessing it so long as they remained a small minority, by giving them the relatively privileged, safer jobs of doing precision work such as shaping fine arrow points. This illustrates the way in which a certain amount of diversity may be actually fostered. It seems quite possible that some genetic characteristics that would be associated with leadership belong in a similar category. But where there is no tendency for sorting the individuals with the distinc-

tive traits out into their respective roles the selection favoring diversity fails to work.

Still another process for maintaining diversity goes into operation in cases in which there is for any reason a premium on the heterozygous type in contrast to both opposite homozygotes. The most cited example of this principle nowadays happens to be the gene for sickle-cell anemia prevalent in parts of Africa. The milder change in erythrocytes occurring in heterozygotes has given evidence of rendering its possessors less suitable as hosts for the virulent type of malaria there present and it frequently saves their lives in this way, yet the mutant gene cannot multiply enough to crowd out the normal gene since when it becomes homozygous its own effects in causing a drastic anemia are fatal. Thus diversity for this characteristic is maintained in this region, but only at the cost of the continual dying out of the numerous homozygotes.

Although there is evidence of the long-continued action of the same mechanism, based on the superiority of the heterozygote, in the case of a number of genes determining antigenic differences, such as those of the blood groups, and the same thing may hold in the case of various other traits, the principle is, fortunately, far from a general one. For if the heterozygous type were in general the superior one the maintenance of each superior type would be possible only at the expense of the continual throwing off of inferiors, and those inferiors would form a more numerous incubus, the greater the relative success of the heterozygotes. The more generally applicable rule is that which we have mentioned earlier—that the heterozygote tends to stand part way in its characteristics, and also in the degree of disadvantage or advantage it confers, between the 2 opposite homozygous types. The exceptional cases of the heterozygote being superior are probably represented for the most part (leaving out a few blood group genes) by adaptations that have not yet stood the test of geological time. For we should expect natural selection in the end to find mutations giving gene combinations which can achieve in homozygous form the same beneficial effects that at first could be attained only by the unstable, wasteful means provided by the selection of heterozygotes.

The phenomenon called heterosis or hybrid vigor is often confused with the one discussed in the two preceding paragraphs, but genetic analysis has given little ground for such identification. The general debilitation, often accompanied by particular disabilities and defects, that is usually found when organisms which ordinarily intercross are inbred, is caused by the bringing together of like recessive mutant genes of detrimental nature. These genes, of course, have far less influence in the heterozygous parents than in their partly homozygous offspring but it is probable that in the great majority of cases the individual homozygous for the normal allele would be superior even to the heterozygote. In small communities, especially where selection has been lax, there has been a more or less accidental accumulation of such genes. That is, the diversity of the types of mutant genes present has decreased through the smallness of the numbers and those types that remain are correspondingly more frequent and more likely to be homozygous, even though the inbreeding may not have been very close. In contrast with this, when the individuals of two such communities, which differ in regard to the recessives that have become prevalent, breed together, their offspring, being homozygous for fewer of the mutant genes (although heterozygous for more of them), approximate more nearly to the ideal "normal" condition.

The above example touches upon another important principle of population genetics: the phenomenon of drift, as Wright has called it, whereby given mutant genes happen to become established in a certain group of individuals without presenting any advantage at all, just as a result of a succession of accidents of multiplication. This process depends purely on the statistical fluctuations to which small numbers are subject and cannot occur to any considerable extent in populations that remain continuously large and thoroughly interbreeding, as our modern populations are tending to be. However, populations that are at times reduced to small numbers, like many of those of the past, are subject to the relatively large variations of these small numbers. Thus a large population derived from a few individuals will tend to exhibit the accidental peculiarities of those individuals. More important than pure drift, however, is the divergence which occurs as the result of the diverse selection act-

ing upon different small groups, for some of these groups are likely later to increase in numbers, retaining these divergences.

In fact, selection in exactly the same direction, acting upon separated small groups living under sensibly the same circumstances, may often achieve very different genetic results, even though these effects may in some cases be outwardly the same. For selection can only operate to eliminate or to multiply those mutant genes that have happened, accidentally, to arise, and to become numerous enough to afford a basis for selection. Since a mutation of any given type, in some particular gene, is an exceedingly rare event, of the order of 1 in 100,000 or 1 in 1,000,000, and since most mutant genes that start as detrimentals fail even as a result of accumulation to attain a frequency of more than 1 in a 1,000, it is obvious that two different small groups, isolated from one another, will usually offer different materials to the selective mechanism. Thus larger populations that may later be derived from them will differ in these respects, and the longer the isolation goes on the further will the inner divergence go, especially since the establishment of one unlikeness tends to favor the selection of another one.

There is evidence, however, that human groups have had enough mobility in terms of geological time, and have engaged in so much mixing, in consequence, as to prevent the indefinitely great accumulation of such differences. For a study of the frequencies of antigenic characteristics to be found in the blood shows clearly the gradual change in these frequencies, as one passes across the great continental areas. Yet despite these imperceptible gradients, certain more conspicuous characteristics, such as stature, coloration, shape of eye, etc., that we associate with recognized races and subraces, change in a sharper and more extreme fashion. It seems likely that these more conspicuous differences have been maintained by a diversity of selection (including sexual selection, which may in part have been influenced by longstanding traditional attitudes) operating in the different areas, even while the general collection of human genes became to a large extent pooled. Today, however, these geographically diverse selective forces are weakening, as our artificial devices, such as sunglasses, vitamin capsules, modern garments, heating and cooling, and so on, are obviating the need for these special biological differentiations. At the same time, it is evident from the results of race crossing that few or no drastic incompatibilities have yet come to exist between the diverse gene systems that have arisen in different regions. The worst such incompatibility that we know of, that in the Rh system, exists *within* the European peoples themselves, and can only be improved—for them but not for those with whom they cross—by their outcrossing.

Our discussion on nondetrimental diversities has been concerned mainly with that category of genes, arising relatively rarely by mutation, which are not prone to be definitely detrimental, or which at least can find some use under certain existing conditions. Even though these genes are so infrequent in their origination, they become very frequent by accumulation just because they have such a low rate of elimination. It is probably these genes rather than the much more frequently arising definitely detrimental genes which, on the occurrence of some change of conditions favoring a different type, usually furnish the material for the next step in evolution.

It is important for the medical man, the educator, the legislator, and all who have to do with the policies shaping the treatment of human beings and the sorts of lives they lead, to be realistic in recognizing the existence of great genetic diversities, both those in the normal range and those caused by the more detrimental genes or by unusual accumulations of the lesser ones. Only by facing these differences, studying them, and diagnosing them, can the course of education, the modes of character training, the kinds of jobs and of living arrangements, the medical treatments, be properly suited to fit these diversities and to give each person the opportunity to make the most of his own nature. Mass methods have only been a first step. We all do have an enormous amount in common, but instead of trying to iron out our differences we ought to try to take advantage of them and to cultivate in beneficial ways their diverse potentialities. Harmony is not uniformity.

IMPROVEMENT FOR THE WORSE?

It would take us too far afield here to analyze the radical changes which modern

civilization has brought in the conditions of selection. Surely the diverse selection occurring in small isolated groups is rapidly on the way out, and even the differences in selective factors between the larger groups are fading. In fact, the whole basis of selection that in the long past has served to bring us to our present estate seems under modern conditions to be in process of disintegration. This fact can be best appreciated if in closing we return to a consideration of our huge load of detrimental mutations.

The existence of this load should not in itself be a cause of alarm, for it dates back more than a billion years. We know that life in this world is necessarily full of imperfections and that it has nevertheless advanced just because new things were tried, of which the majority failed but the small minority succeeded in a relative sense. The ground for concern lies in nearly the opposite direction: in the fact that our scientific and social advances, our artificial aids to living, our therapies and our prophylaxes, are enabling us to counteract to a considerable extent the harmful effects of many mutant genes, and thus to retard their elimination and foster their accumulation, while at the same time some of our physical practices, such as the increasing use of radiation, are causing an accelerated production of mutations.

The obvious defense for our ameliorative procedures is that we can afford the resultant increase in our load of mutations since we have lessened the damage done by the individual mutations. Unfortunately this argument overlooks the fact, previously discussed, that in the long run mutations having only a small harmful effect do about as much damage to a population as an equal number of highly injurious mutations, because the small deviations accumulate so much more as to give rise, in the end, to just as heavy a load of disability as the large ones. This means that our modern methods are causing the load of mutations slowly to rise, and that this rise must continue until, even with all present and future aids to living in active operation and consuming a maximal proportion of our efforts, we will again be having as many failures in life, resulting from genetic inadequacies that can no longer be held at bay, as had plagued mankind in his old prescientific days. In other words, the mere maintenance of the level of infelicity characteristic of primitive man would then be possible only by the full use of all our artifices. This procedure would constitute a social burden even more onerous than the rigors of primitive life.

All this illustrates the principle that the prevailing harmfulness of mutations results in a downward pressure toward deterioration that only selection finally counteracts. When, as in some parasites, any organ or trait can be dispensed with and is no longer actively maintained by natural selection—that is, by the dying out of the mutants that weaken that organ—then the organ gradually subsides and is lost. It is possible to circumvent this principle only by substituting artificial selection for natural selection. In the human species this would mean the institution of social and economic conditions, mores, motivations, and an educated understanding, of such a nature as to lead men and women to regard reproduction as essentially a social service, constituting one of their most important contributions to society, and to lead them at the same time to accept a realistic appraisal of genetic values, including those applying to themselves.

Such a revolution in outlook and in resultant practices, which I believe will eventually come about with a spread of education in these matters, would not only tend to prevent genetic deterioration but even to promote genetic improvement. In such a situation, all advances made in therapy, hygiene and, in general, in the "art of living," could only redound to the increase of human well-being. For they would no longer carry in their train the enervating aftermath of a compensatory increase in the mutational load. If we do not hitch our wagon of humanity to this star of controlled reproduction it will inexorably although perhaps imperceptibly roll down hill, despite all our efforts in the opposite direction, or rather, as an indirect consequence of those very efforts at improvement.

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THE MOLECULAR BASIS OF GENETICS[1]

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I am sure that most mental disease is chemical in origin, and that the chemical abnormalities involved are usually the result of abnormalities in the genetic constitution of the individual. I think that it is probable that mental illness often results from a *quantitative* biochemical abnormality—the presence in the individual of molecules of a substance that is normally present, but in concentrations somewhat larger or somewhat smaller than normal. Presumably, the manufacture or the retention of the substance in too large amount or too small amount is often the result of the genetic constitution of the individual, although in some cases it may be attributed to his environment—for example, to the nature of the food that he eats. On the other hand, mental deficiency seems to be often the result of a *qualitative* abnormality: the presence in the patient of molecules that differ in their structure from those present in a normal human being. The manufacture of abnormal molecules of this sort is determined by the genetic constitution of the patient; the disease is inherited. A disease of this sort, caused by molecules of abnormal structure present in the patient in place of the molecules of normal structure that are present in normal human beings, is called a molecular disease.

The expression molecular disease is here used in a special way. All human beings are made up of molecules, and in a sense one might say that all diseases involve these molecules, and perhaps also the molecules that make up bacteria and viruses, and that accordingly all diseases are molecular diseases. The restriction of the expression molecular disease to diseases that are due to abnormal molecules, differing somewhat in structure from related molecules that are present in normal human beings, seems to me a useful one.

Sickle-cell anemia was the first disease to be shown to be a molecular one(1). In this disease the red cells of the blood are twisted out of shape, when they are in the venous circulation—they regain their normal shape in the arteries. The twisted red cells become sticky, they clump together, and sometimes interfere with the flow of blood to some parts of the body and cause damage by anoxia; they are also rapidly removed from the circulation, causing the patient to become anemic. The disease seems to be a disease of the red cell, a cellular disease; however, it was found that in fact the hemoglobin molecules manufactured by the patient are abnormal, differing significantly in their structure and properties from the hemoglobin molecules manufactured by normal individuals, and it is clear that the disease is a disease of the hemoglobin molecule.

Although the complete molecular structure of sickle-cell-anemia hemoglobin is not known, nor, in fact, the structure of normal hemoglobin or any other protein, the way in which the molecular abnormality causes the manifestations of the disease sickle-cell anemia is clearly understood. The molecules of the sickle-cell-anemia hemoglobin have such a structure that they clamp on to one another easily, to form long rods, which line up side by side to produce a liquid crystal of the nematic type. As this liquid crystal grows inside of the red cell, it becomes longer than the diameter of the cell, and in its continued growth it twists the cell out of shape.

There is strong evidence that the combination of the molecules of sickle-cell-anemia hemoglobin with one another is caused by a detailed complementariness in structure of one part of the molecule and another part of the molecule, so that the weak intermolecular forces that operate between protein molecules in general are able to collaborate when the surface region of one molecule comes into juxtaposition with the complementary surface region of a second molecule, forming a bond that holds the molecules tightly together. This complementariness in structure is destroyed when the hemoglobin molecule

[1] Read in the theoretical symposium on "Recent Progress in Genetics and its Implication for Psychiatric Theory" at the 112th annual meeting of The American Psychiatric Association, Chicago, Ill., April 30-May 4, 1956.

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combines with oxygen, and accordingly the process of sickling of the cells is reversed when the blood is oxygenated.

One of the properties in which sickle-cell-anemia hemoglobin differs from normal adult human hemoglobin is the electric charge: molecules of the two kinds of hemoglobin differ from one another by about 3 electronic charges. The way in which sickle-cell-anemia hemoglobin was recognized as a substance with different molecular structure from normal adult human hemoglobin was the measurement of the mobility of the two hemoglobins in an electric field, using the Tiselius electrophoresis apparatus. The genetic origin of the molecular abnormality was clearly indicated when the hemoglobin from the parents of a sickle-cell-anemia patient was studied. The hemoglobin of each parent was found to consist of a mixture of approximately equal amounts of the two kinds of hemoglobin. Accordingly, the parents were identified as heterozygotes, containing two allelomorphic genes at some level in a pair of chromosomes. One of these genes manufactures normal adult human hemoglobin, and the other one manufactures sickle-cell-anemia hemoglobin. The parents are in good health, so far as the anemia is concerned—the dilution of the abnormal hemoglobin by the normal hemoglobin prevents the sickling process from occurring in the heterozygotes, except under unusual conditions, as at very high altitudes, where the partial pressure of oxygen is low. When two of the heterozygotes, the carriers of the sickle-cell-anemia gene, marry, one-quarter of their children may be expected to have the disease sickle-cell anemia, one-quarter to be normal, and one-half to be carriers like the parents.

The question of the continued high incidence of the sickle-cell-anemia gene, despite its continued loss because of the lethal character of the homozygous condition, has been raised by Neel(2), who suggests 3 alternative explanations: (1) continued production of the sickle-cell-anemia allele through mutation; (2) the existence of an abnormal genetic mechanism that favors the heterozygous condition over the normal condition; (3) a positive selection of the heterozygotes, perhaps through increased fertility. The first explanation must be rejected because the rate of mutation that would be required is far greater than any that has ever been observed for any organism. There now exists evidence indicating that the third alternative provides the correct explanation, and that malaria is involved. It was first suggested by Brain(3) that the nature of the red cells in the sickle-cell-anemia carriers might give protection against malaria parasites, and thus confer an advantage that would balance the disadvantage of the lethal homozygosity. A test of the hypothesis was carried out by Allison(4), who infected 15 healthy adult Africans with sickle-cell-anemia heterozygosity and 15 similar healthy adult Africans with normal hemoglobin with *Plasmodium falciparum* by subinoculation with 15 ml. of blood containing a large number of trophozoites or by allowing them to be bitten by heavily infected anopheles mosquitoes, in which the presence of sporozoites was confirmed by dissection of the mosquitoes. The infection was established in 14 out of the 15 Africans without the sickle-cell-anemia heterozygosity, and in only 2 of the 15 normal Africans. It was concluded by Allison that the abnormal erythrocytes of the heterozygous individuals are less easily parasitized by *P. falciparum* than are normal erythrocytes, and that accordingly those individuals who are heterozygous for the sickle-cell-anemia allele have a selective advantage over normal individuals in regions where malaria is hyperendemic.

It is, of course, not unreasonable that the abnormal hemoglobin might be less effective than normal hemoglobin in nourishing the parasites; moreover, it is known that the parasitized erythrocyte uses up oxygen 100 times as fast as a normal erythrocyte, and it might be expected, as suggested by Allison, that the de-oxygenated erythrocyte would sickle, and thus crush the parasite. Accordingly, we have a molecular mechanism not only for the disease sickle-cell anemia, but also for the protection that the heterozygous condition provides against malarial infection.

Since the discovery was made of the first abnormal hemoglobin, about 10 more have been discovered, and about a dozen diseases, kinds of hereditary hemolytic anemia, have been recognized as caused by these abnormal hemoglobins.

I think that it is likely that many kinds of mental retardation are molecular diseases,

caused by the gene-controlled manufacture by the patient of abnormal molecules in place of normal ones that are manufactured by normal individuals. There is strong indication that phenylpyruvic oligophrenia is a molecular disease, or perhaps a complex of molecular diseases. The investigations of Fölling, Jervis, and others have shown clearly that phenylpyruvic oligophrenia is the result of a homozygous genetic abnormality that affects an enzyme that normally catalyzes the oxidation of the amino acid phenylalanine to tyrosine. The patients with phenylpyruvic oligophrenia are not able to carry out this oxidation effectively; they do not manufacture an effective enzyme to catalyze the reaction. We may infer that the patient has inherited from each of his parents an abnormal gene, which leads to the manufacture of an abnormal molecule in place of the normal enzyme. The alternative is that there is a block in the process of synthesis of the enzyme, so that nothing at all is manufactured—it may not be important to differentiate between the failure to manufacture the enzyme and the ability to manufacture an abnormal molecule that is not able to perform the catalytic function of the enzyme.

The first step in solving a problem is to understand it. The discovery of the abnormal hemoglobins has provided us with a far deeper understanding of the hereditary hemolytic anemias than existed before. In the same way, much may be done in increasing our understanding of phenylpyruvic oligophrenia. It may be found that there are many different allelomorphic genes that can contribute to the production of the disease; that is, that these genes, in homozygous state or double heterozygous state, may produce any one of a large number of somewhat different conditions that are now grouped together, and that some of the patients who manufacture abnormal enzyme molecules that retain a certain amount of catalytic activity may be susceptible to treatment. A test that would distinguish the carriers of phenylpyruvic oligophrenia would be useful; in particular, the sibling of a phenylpyruvic oligophrenic patient could learn whether or not he is a carrier of the gene, and whether or not he should avoid marrying another carrier.

A few months ago, when I gave the Edsel B. Ford Lecture(5), I mentioned that a score of diseases have so far been recognized as enzyme diseases, presumably resulting from the manufacture of abnormal molecules in place of the active enzyme molecules, and that it seems to me not unlikely that there are thousands of such diseases. I continued by saying that I foresee the day when many of these diseases will be treated by the use of artificial enzymes. When our understanding of enzyme activity becomes great enough—and this will require that a determination be made of the detailed arrangement of the thousands of atoms that make up one of the molecules of the enzyme—it will be possible to synthesize a catalyst for the oxidation of phenylalanine to tyrosine. A small amount of this catalyst may then be attached to a reticular framework inside of a small open-ended polythene tube, which can be permanently placed in an artery of a new-born child who has been shown by the presence of phenylpyruvic acid in the urine to have inherited phenylpyruvic oligophrenia; through the action of the catalyst the child should then develop in a normal way. This idea seems fantastic now; but the world of 1955 is a fantastic world from the viewpoint of 1905, and I have little doubt that my prediction about the world of 2005 will turn out not to be a bold one, but rather a timid and unimaginative one.

These hereditary diseases involve the genes—abnormal genes, abnormal molecules that we can now safely identify as molecules of deoxyribosenucleic acid. Recent advances in knowledge about the structure of deoxyribosenucleic acid have provided the basis for confident speculation about the molecular nature of the processes of heredity. For 15 years there has existed strong support for the belief that biological specificity in general involves a detailed complementariness in structure of interacting molecules(6), and the proposal was made 10 years ago(7) that the mechanism of self-duplication of the gene is a 2-stage mechanism involving the use of a molecule A as the template for the synthesis of a complementary molecule A^{-1}, and and then the use of A^{-1} as the template for the manufacture of a molecule complementary to it and identical with A. Watson and Crick(8) then made an extraordinarily at-

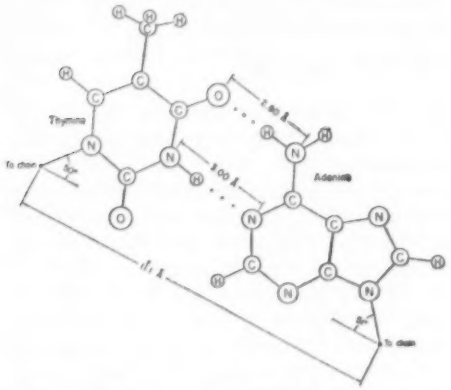

FIG. 1.—Diagram showing complementariness in structure of thymine and adenine, which form 2 hydrogen bonds with one another.

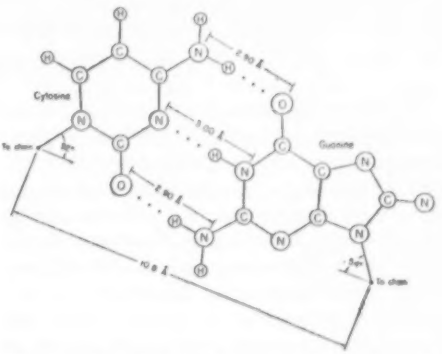

FIG. 2.—Diagram showing complementariness in structure of cytosine and guanine, forming 3 hydrogen bonds.

tractive and stimulating proposal about the structure of deoxyribosenucleic acid. They showed that the x-ray diffraction pattern given by fibers of deoxyribosenucleic acid is compatible with a proposed structure involving 2 deoxyribosenucleic acid chains, coiled about one another to form a double helix. In each chain there are residues of one of the 4 nitrogen bases, adenine, thymine, guanine, and cytosine, at positions every 3.3 Å along the axis of the double helix. The structure is of such a nature that at each level the nitrogen bases of the 2 residues combine with one another through the formation of hydrogen bonds. The stable hydrogen-bonded structures that can be formed are only 4 in number: they involve having one or another of the 4 pairs, adenine-thymine, thymine-adenine, guanine-cytosine, or cytosine-guanine, at each level. The nature of the hydrogen bonds formed by these pairs is shown in Figs. 1 and 2 (these figures are from a paper by Pauling and Corey (9); they differ from the proposal by Watson and Crick in showing 3 hydrogen bonds between guanine and cytosine, rather than only (2). Accordingly the distribution of the 4 nitrogen bases along one polynucleotide chain is completely determined by that along the other: if adenine occurs at a given level in one chain, thymine must occur in the other, and so on. The molecular mechanism of inheritance proposed by Watson and Crick is accordingly that the double helix is untwisted, and each of the polynucleotide chains, A and A^{-1}, then serves as the template for the manufacture of its complement, A^{-1} and A, respectively. Although there are many details that need to be worked out, and some significant changes in this picture may well have to be made, there is no doubt, in my opinion, that Watson and Crick have made a contribution of great importance, and that we are now ready to attempt to formulate a completely detailed molecular mechanism of heredity, and to work out a thorough understanding of disease in terms of molecules. I am confident that, in particular, there will be rapid progress in the field of mental retardation and mental illness, during the coming decade.

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THE GENETICS OF HUMAN BEHAVIOR [1, 2]

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Experimental biologists are safely entrenched in the age-old esteem for progress through science and can well afford to withhold comments on the cultural and behavioral aspects of morphologic inequalities among people. It is only when such an investigator invades that particular province of psychiatry where belief in heredity in relation to personality development is equated with lack of empathy or a depraved social conscience that a sinister tinge accrues to him and his work(11, 19, 24).

In the face of such a 2-valued system of conceptualization and terminology, connoting either trust or distrust in man's perfectibility, even a truly liberal psychiatrist with genetic leanings finds it difficult to cast off the onus of being an unempathetic metascientist. To be sure, were he to feel called upon to express codified value judgments regarding the original goodness or sinfulness of mankind(22), he would be out of bounds. However, it is not his fault if his investigative data arouse so much disquietude that they need a de-emotionalized climate in which to be assimilated. Meanwhile, to balance the scales, there are zealous research workers everywhere who are ardent in their views, despite the fact that they have not had the benefit of genetic training.

In the search for the roots of human behavior, it would be well to stay clear of dichotomous absolutes. In particular, the interaction of heredity and environment is formulated as a meaningless antithesis as long as vague abstractions are used in describing the properties of an organism that is most certainly both active and reactive.

Man, to be sure, mirrors his culture and the social configuration of his parental home. Yet he also forms an autonomous functional unit that perpetuates itself as the matrix of his hierarchically organized traits and self-assertive acts. The human infant, if normally endowed, is certain to possess those structural, functional, and behavioral potentialities that distinguish individuals of the human species from those of any other(15, 17). While the emergence of his individuality will depend in part on the nutritive capacities of his family group, the constructs of his mind are at no stage like a hollow shell or a *tabula rasa*, as Locke would have it(4).

In a more eclectic scheme of human personality development, the importance of genic elements in the organization of behavior patterns rests on the interdependence of organic structure and psychologic function throughout the life of the individual. There is no behavior without an organism, no organism without a genotype, and no physiologic adaptedness without continuous and integrated gene activity.

Environmental influences are vital, and after conception they gain coequality with those arising from heredity. However, only within the limits set by the genic constitution of the organism can external factors have an effect on the dynamics of physiologic functions and interactions. Beyond these limits, no power plant exists for generating behavioral potentials. Such basic phenomena as growth and maturation, homeostasis and adaptation, reflexive behavior and constitution remain chameleonic allegories without the solid foundations of genetic principles.

Man, in order to be able to maintain his present evolutionary level, must be both conditionable by culture and impressible by education. The ability to learn from others and to profit from experience is determined by the genotype, while cultural values and opportunities have to be acquired by each individual through communication with his group. Variations in basic traits are inherited to the extent that they are end-products of a chain reaction set in motion by genes.

The effect of a gene expresses itself through the control of a specific enzyme which spurs on the production of a unit dif-

[1] Read in the theoretical symposium on "Recent Progress in Genetics and its Implications for Psychiatric Theory" at the 112th annual meeting of The American Psychiatric Association, Chicago, Ill., April 30-May 4, 1956.

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ference in development or function. The outcome of this action is subject either to reinforcement or interference by nonallelic genes, that is, other genes which are not located at the same point of a chromosome.

Conversely, the occurrence of different mutants of the same gene at any one locus makes it possible for the given point to control various normal and abnormal versions of a trait. In fact the demonstration of specific pathologic changes producible by a mutant gene provides adequate proof of the existence of a normal allele. The action of the normal gene can be assumed to play an indispensable part in maintaining health and normal behavior, even if its biochemical equivalents have yet to be identified. Therefore, it is just as unfair to blame heredity for only the unpleasant events in life, as it is to hold the genes responsible for every unusual mode of behavior whose origin is still in the dark.

Broadly formulated, then, a person's phenotype may be defined as the visible expression of his moldability by environmental influences, while it is his genotype that determines his norm of reaction to the total range of possible environments during his lifetime. The implication here is that every gene-controlled mode of activity requires an operational area in which to unfold (9, 18, 23, 28, 31).

Since no part of this environmental area of operation is inert, in the sense of being ineffectual where the behavioral responses of the individual are concerned, appreciation of environmentally produced variations in the expression of gene-specific behavior components is clearly as essential to an understanding of heredity as is the knowledge of geometry to that of mathematics. Except for real instincts, which need not be learned, it is axiomatic that no type of behavior is controlled entirely by genic elements, nor is it ever the result of a single cause, genetic or nongenetic (5, 7, 33). Estimates of individual contributions are meaningful only when viewed against the backdrop of the total genetic and environmental variation observed in a population.

It has already been mentioned in this symposium that some traits occur more often in one population than in another, depending on the relative frequency of a gene in different populations. Also, noninstinctive responsiveness to conditioning influences varies in different stages of development, and from person to person at a comparable stage of development (7, 13). The aggregate of gene-specific personality constituents is so vast, and the number of interactive variables in the shaping of a behavior pattern so infinite, that every individual can count on being unique—identical twins excepted.

The gene-specific uniqueness of man's individuality is now recognized in all branches of the behavioral sciences, even if the parliamentary Bill of Acceptance has yet to be ratified by some. What differs most are the descriptive labels affixed to this uniqueness. For instance, the differentiation of early behavior patterns has been described as an "ordered sequence" that begins with the establishment of reflexive responses and gradually leads through progressive stages of maturing to the development of coordinated motor, perceptual, and intellectual functions (6); or as "hierarchical organization of traits," in the course of which the infant will in time develop a conscience and a sense of self (4); or as a process of "biosocial integration with the total family configuration" (1). Other genetic phenomena have been referred to as the result of an innate equipment "with specific power plants and tools" (25) and as a biologically determined trend toward security and homeostatic stability, identified with a striving for "survival with a minimum amount of expenditure" (2).

Despite these differences in terms used to describe the interaction of genetic and nongenetic components of behavior, there is interdisciplinary agreement on at least one general premise; namely, that those aspects of the environment which are potent in affecting the organism depend not only on the degree of maturity the organism has attained, but also on its ability to cope with extrinsic hazards. Another point of unanimity is the belief that many children are capable of working out fairly adequate ways of dealing with difficulties in their home milieu and interpersonal relationships. By the same token, the established interdependence of social aspirations and biologic needs would seem to impose certain limits on the diversity and reach of human motives and the sublimating endeavors taken up by self-determination.

Genetically, a chaotic lack of uniformity

in human societies is prevented by various principles of selection, and by the fact that the cultural forces which mold, as well as the formative elements which secure moldability on the human level, are actually end-products of the same evolutionary process. Viewed in this light, they are like the 2 sides of a coin, defying analysis as independent variables(10, 12, 26). Hence, the inability to separate the 2 sets of determining factors can only in part be ascribed to the parental practice of rearing one's own children. It is more than likely, too, that this virtual inseparability will last as long as our knowledge of the constituents of the coin remains as limited as it is at present. A reflection of this state of affairs is seen in the fact that most test devices for measuring meaningful personality differences have proven refractory to standardization(8, 18, 21).

Apart from unavoidable limitations on the assessment of gene-specific personality components, the twin study method represents an excellent comparative procedure for demonstrating the significance of heredity in many behavior variations, both normal and abnormal. The effectiveness of the method is matched by its economy and versatility as a sampling procedure for investigating traits, which require vertical and longitudinal comparisons under controlled conditions, and personal contact with families from various population groups, including some whose private affairs might otherwise not be open to research. Procedurally, it is no real disadvantage that twins cannot be separated before they are born, or that they cannot be provided with 2 mothers of different age, personality, or health status.

The popular notion that the behavior patterns of 1-egg twins are alike chiefly because of unusual similarity in their early environments has yet to be substantiated. If confirmed, the argument would only strengthen, rather than weaken, any correctly formulated genetic theory. Psychodynamic concepts, too, are built on the premise that man is selective in respect to important aspects of his life experiences and so can be thought of as "creating his own environment"(2). Utilization of our "own potential formula of adjustment" evidently depends on what Sanford(27) calls the body's ability "to function at its own built-in best." Plainly, each of these elegant allegories conveys a genetic idea.

In the area of normal personality variations, gene-specific derivations have been shown by comparative twin data to range from physical, coordinative, physiognomic, and temperamental characteristics to intellectual abilities, affective regulations, and special talents(6, 14, 16, 29, 32, 34). In between are sex maturation patterns, variations in antibody production and neurohormonal alarm reactions, the capacity for longevity, and the ingredients for sustained tolerance of physiologic or psychologic stress, a highly essential prerequisite for a well-balanced personality(17, 20, 30). It is well known that each individual has his own threshold of adaptability to different types of stress, and his own pattern of stress symptom formation.

Consistent similarity in the composition of these personality components is not found in the absence of genotypic similarity. Two-egg twins of the same sex tend to differ as much in their personalities as do any siblings reared together or apart. In 1-egg twins, even pronounced differences in life experiences, however adverse, are rarely potent enough to erase basic similarities in appearance and general personality traits. The brief histories of a few typical twins may help to illustrate this point.

The 2-egg pair from an average middle-class home, shown in Fig. 1, falls within the normal range, despite striking dissimilarities in physical and mental development. Before puberty, the girls differed in height by 4 inches, in weight by 42 pounds, and in intelligence quotient by 22 points. The bright girl is no longer as thin as she used to be, nor as constricted in the emotional sphere. Possessed of strong intellectual strivings, she is doing well in an academic course, while her dull-normal, belligerent, and emotionally immature twin sister has trouble with her commercial course.

The 1-egg twins in Fig. 2 come from the same locality and socio-economic background as the preceding pair. Both honor students now in college, they are still indistinguishable either by their appearance or any of their test performances. Except for minor fluctuations in their degrees of maturity and self-reliance, no real difference has emerged between their equally pleasant and well-balanced personalities.

The persistence of similar trends in the integrative and adjustive capacities of 1-egg twins is illustrated by the 24-year-old college graduates shown in Fig. 3. Although one of them has been severely handicapped by a spastic-paralytic form

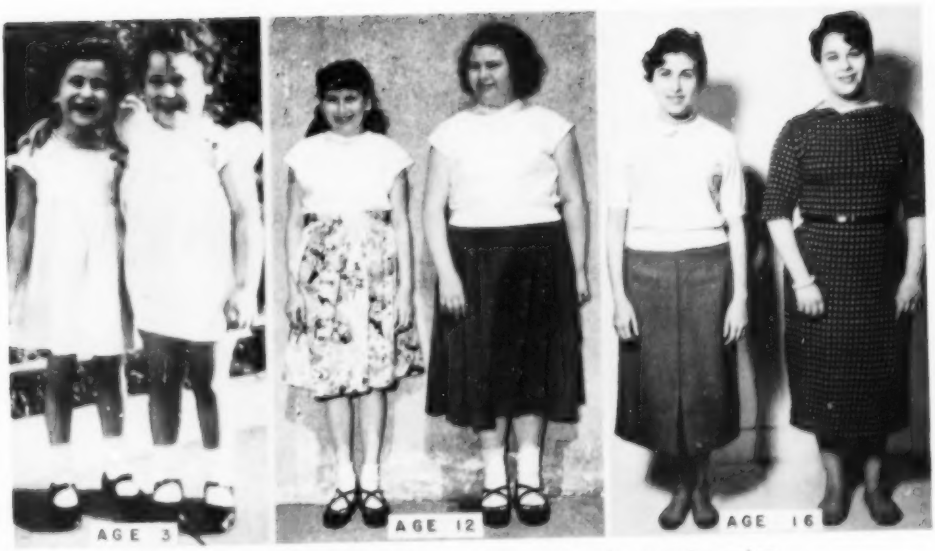

FIG. 1.—Developmental differences in two-egg twins reared together.

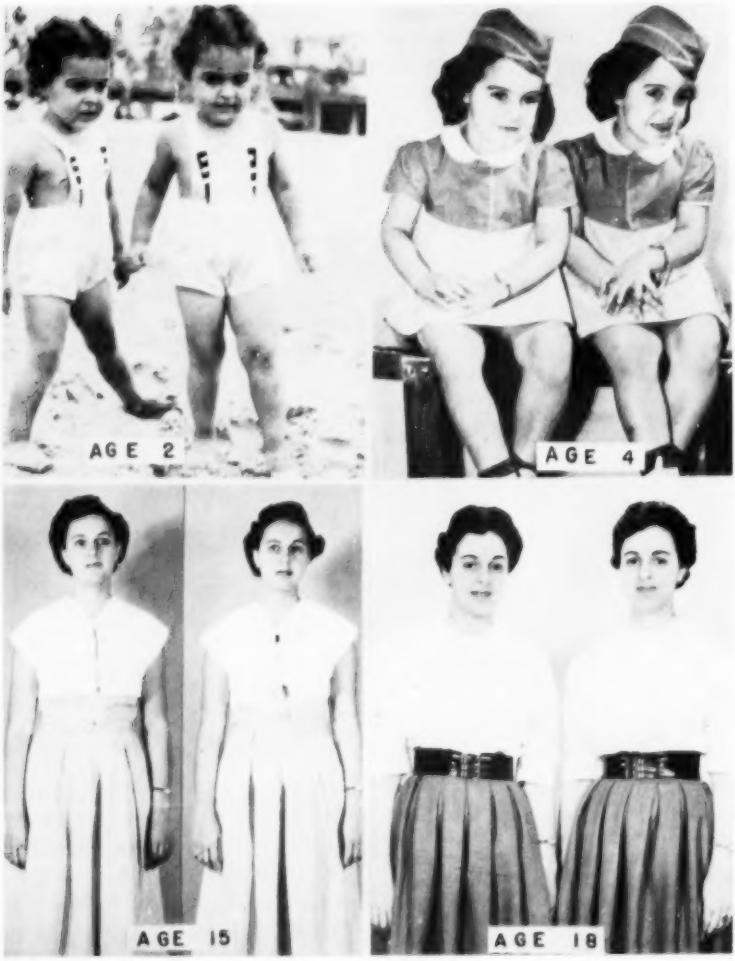

FIG. 2.—Similarities in one-egg twins reared together.

FIG. 3.—Monozygotic twins discordant as to cerebral palsy.

FIG. 4.—Monozygotic twins discordant for deafness.

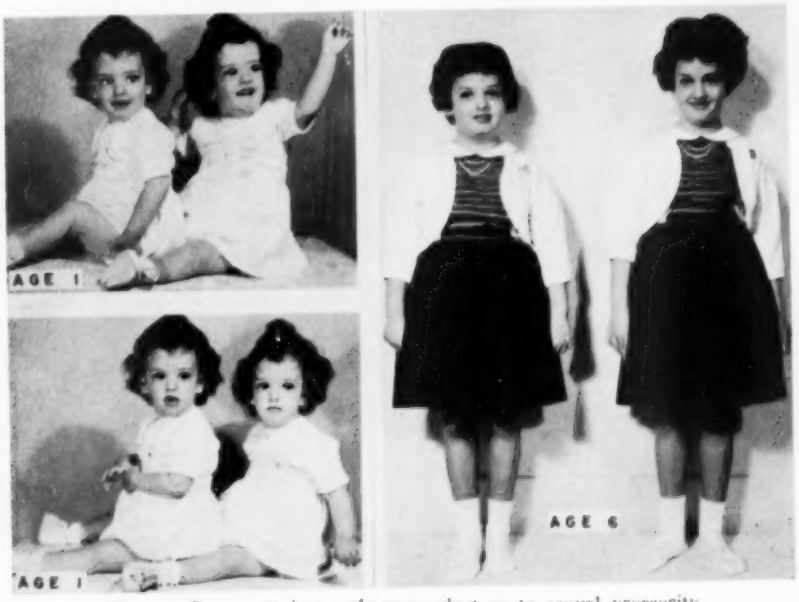

FIG. 5.—One-egg twins partly concordant as to sexual precocity.

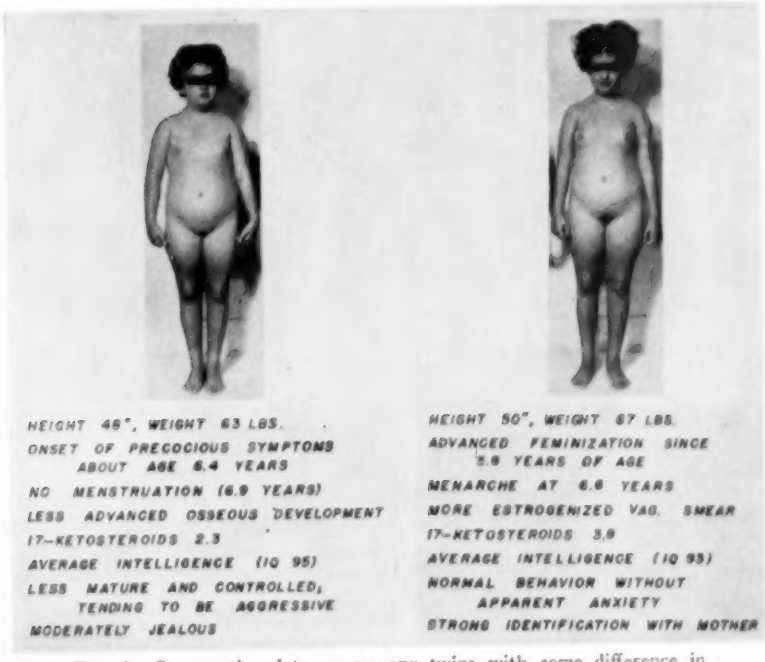
HEIGHT 48", WEIGHT 63 LBS.
ONSET OF PRECOCIOUS SYMPTOMS ABOUT AGE 6.4 YEARS
NO MENSTRUATION (6.9 YEARS)
LESS ADVANCED OSSEOUS DEVELOPMENT
17-KETOSTEROIDS 2.3
AVERAGE INTELLIGENCE (IQ 95)
LESS MATURE AND CONTROLLED, TENDING TO BE AGGRESSIVE
MODERATELY JEALOUS
HEIGHT 50", WEIGHT 67 LBS.
ADVANCED FEMINIZATION SINCE 5.6 YEARS OF AGE
MENARCHE AT 6.6 YEARS
MORE ESTROGENIZED VAG. SMEAR
17-KETOSTEROIDS 3.9
AVERAGE INTELLIGENCE (IQ 93)
NORMAL BEHAVIOR WITHOUT APPARENT ANXIETY
STRONG IDENTIFICATION WITH MOTHER

FIG. 6.—Comparative data on one-egg twins with some difference in sexual precocity (age 6½).

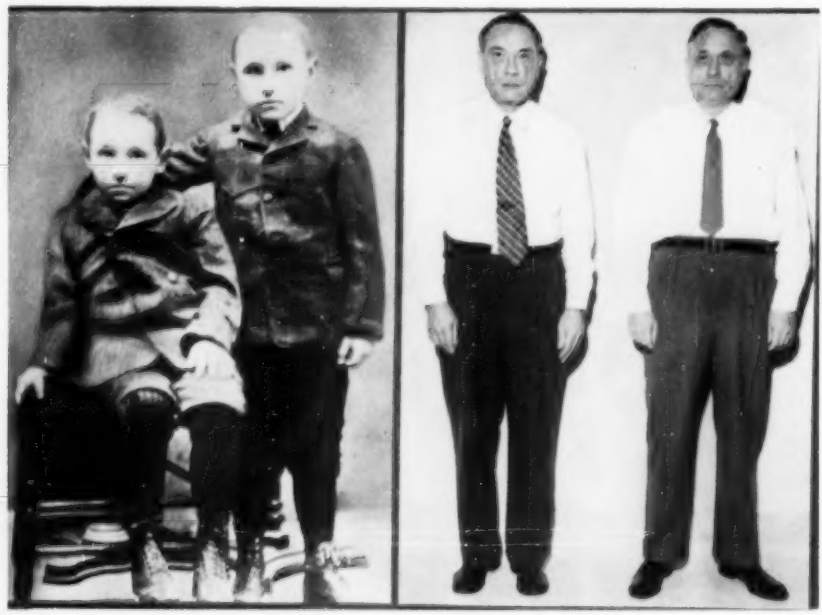

FIG. 7.—The Z twins at the ages of 8 and 60 years.

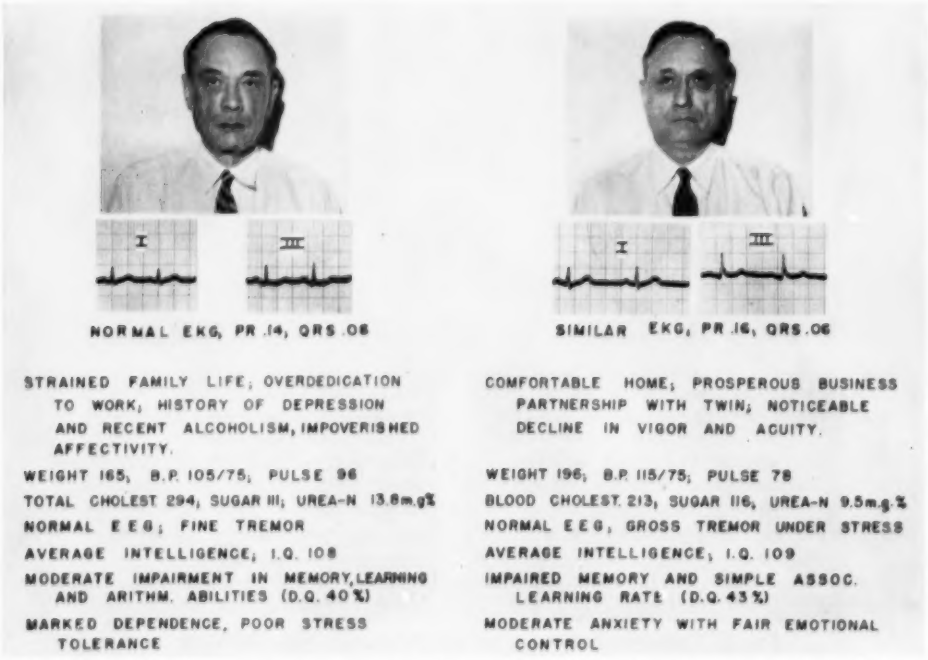
I
III
NORMAL EKG, PR .14, QRS .08
I
III
SIMILAR EKG, PR .16, QRS .06
STRAINED FAMILY LIFE; OVERDEDICATION TO WORK; HISTORY OF DEPRESSION AND RECENT ALCOHOLISM, IMPOVERISHED AFFECTIVITY.
WEIGHT 165; B.P. 105/75; PULSE 96
TOTAL CHOLEST 294; SUGAR 111; UREA-N 13.8m.g%
NORMAL E.E.G.; FINE TREMOR
AVERAGE INTELLIGENCE; I.Q. 108
MODERATE IMPAIRMENT IN MEMORY, LEARNING AND ARITHM. ABILITIES (D.Q. 40%)
MARKED DEPENDENCE, POOR STRESS TOLERANCE
COMFORTABLE HOME; PROSPEROUS BUSINESS PARTNERSHIP WITH TWIN; NOTICEABLE DECLINE IN VIGOR AND ACUITY.
WEIGHT 196; B.P. 115/75; PULSE 78
BLOOD CHOLEST. 213; SUGAR 116; UREA-N 9.5m.g.%
NORMAL E.E.G., GROSS TREMOR UNDER STRESS
AVERAGE INTELLIGENCE; I.Q. 109
IMPAIRED MEMORY AND SIMPLE ASSOC. LEARNING RATE (D.Q. 43%)
MODERATE ANXIETY WITH FAIR EMOTIONAL CONTROL

FIG. 8.—Comparative data on one-egg twins discordant as to reactive depression and alcoholism.

of cerebral palsy, both young men have reached nearly the same level of superior intellectual ability and emotional equilibrium. In spite of considerable difficulty with speech, motor coordination, visual imagination and the handling of nonverbal material, the spastic twin is friendly, efficient in his office work, and gets along well with people. A notable difference between the twins is in their attitude toward religion, the spastic being the one who takes a very active interest in it.

Equally remarkable are the 2 girls in Fig. 4. Although they are 1-egg twins whose parents are both deaf, early total deafness manifested itself in only one of the pair. Both girls are friendly, alert and well-behaved, and on the Vineland Social Maturity Scale achieve about the same level of performance. The deaf twin, before she reached the age of 2, had a habit of tearing out her hair whenever she was angry. Gradually, however, like her hearing twin she learned to vent her fury on the more impervious fur of her toy rabbit.

In another pair (Figs. 5 and 6), a different stress situation arose from body changes associated with isosexual precocity. The taller twin developed signs of early feminization before her sixth birthday and began to menstruate at the age of 6½, followed 6 months later by the development of similar symptoms in the other twin. In the absence of any detectable organic lesion in the brain or ovaries, precocious puberty would here seem to be an extreme constitutional variation set off by hypothalamic influences.

The present difference in osseous development and sexual precocity (Fig. 6) is not matched by corresponding discrepancies in intellectual performance or emotional adjustment. Although the more matured twin seems to show less curiosity about the body, and a stronger identification with the mother, neither girl is noticeably perturbed by an experience for which they were sufficiently prepared.

The adjustive disparity that developed in the sturdy twins shown in Figs. 7 and 8 was precipitated by a malignant schizophrenic psychosis in the wife of one of them. After years of struggling against the disintegration of his home and business interests, the luckless twin at the age of 53 became despondent and began to drink excessively. Incidental to these complications were over 60 electroshocks and bilateral breast operations necessitated by prolonged cortisone medication.

Residual corollaries might be seen in any of this twin's present symptoms, which include impoverished affectivity, impaired memory, extreme emotional dependence, poor stress tolerance, and a considerable loss of weight (Fig. 8). The only trouble is that the other twin, without a comparable history, shows nearly the same degree of impairment in memory and intellectual functions, gross tremor under stress, and even a slightly higher deterioration quotient. On the whole, the contrasting life situations of the twins have not obscured the remarkable similarities in their basic personality characteristics.

As to behavior disorders that are not sufficiently explained on a situational or experiential basis, the list of conditions for which complete twin sibship data are now available is headed by the schizophrenic and manic-depressive types of psychosis. Since these 2 disorders do not occur interchangeably in the same twin pairs, they are assumed to be genotypically specific. The potentialities for a cyclic psychosis are probably associated with a subtle disturbance in a neurohormonal control mechanism which ordinarily protects a person from having harmful extremes of emotional responses.

While the tendency to exceed the normal range of mood alterations apparently requires the mutative effect of a single dominant gene with incomplete penetrance, the metabolic deficiency in a potentially schizophrenic person is most likely the result of a recessive gene. The disordered behavior pattern produced by this specific vulnerability factor is not correlated with inadequacy of the parental home in a simple manner, but is subject to modification by mesodermal defense reactions. Psychodynamically, the pattern has been described as an integrative pleasure deficiency leading to adaptive incompetence (25).

Involutional melancholia and other nonperiodic forms of depressive behavior in the involutional and senile periods have been shown by twin family data to be unrelated to the manic-depressive group of disorders. There is an indirect link with the schizophrenic genotype through certain forms of emotional instability characteristic of schizoid personality traits. Other symptoms of maladjustment in the senescent period may arise either from gene-specific metabolic dysfunctions peculiar to the senium, or from graded differences in general health and survival values.

Homosexual behavior in the adult male continues to yield a higher 1-egg concordance rate than any of the other conditions investigated. This finding points to a disarrangement in the balance between male and female maturation patterns, resulting in a shift toward an alternative minus variant in the integrative process of psychosexual maturation.

Another condition with a well-established

monozygotic concordance rate of close to 100% is an entirely different defect of more obvious organicity, namely, mongolism(3). Since the corresponding rate for 2-egg cotwins does not exceed that of their later-born siblings (approximately 4%), the search for the etiologic factor in mongolism is narrowed down by twin data to a more or less permanent change in the mother's endocrine or reproductive system. Evidently, the noxious influence during a mongoloid pregnancy cannot be transient, but acts on a genetically predisposed embryo, or upon the ovum, or upon the embryo prior to the earliest stage when twinning occurs by division.

In regard to all these disorders, twin family studies are helping materially to focus attention on persisting obscurities in their etiology. Generally, the objective of genetic investigations in man is not only to demonstrate that gene-controlled phenomena play a role in the differentiation of normal and abnormal behavior patterns, but to determine how this action takes place.

In conclusion, it may be said with some measure of satisfaction that recent progress in genetics has been encouraging. Although exact studies of the subject only began at the turn of this century, advances in the cellular, structural and metabolic areas of personality organization have been remarkable. An immediate result has been the improvement of our knowledge regarding the interacting bipolarity of human life. Growing insight into this interaction will gradually unfold a better understanding of human behavior. Somewhere along this line it will be possible to explain variable behavior patterns in terms of physiochemical processes powered by genic elements.

Once this goal has been reached, psychiatrists and other workers in the behavioral sciences will no longer hesitate to welcome geneticists as allies in interdisciplinary studies of human frailties and capacities. Only then may modern man begin to recognize his potential ability to plan his own future, as well as that of the world around him. In consequence, he may learn to exercise his obligation of self-determination in this direction.

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DISCUSSION OF THE GENETICS SYMPOSIUM

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Our Association is fortunate in having present today distinguished guests who have been able to call our attention to some of the new developments in genetics, a science basic to psychiatry, which will inevitably, over time, alter a few of our views about how best to care for our patients. It seems probable that these changing attitudes will be rather subtle, more concerned with proper perspective and proportion than with gross replacement of current beliefs. The remarkable recent advances in experimental and population genetics demonstrated by Drs. Muller and Pauling encourage us to look ahead to some of the probable directions to which their work will lead us and, perhaps, give us a glimpse of the consequences.

The phenylalanine studies by Dr. Pauling call attention in an emphatic manner to the "well-known" fact that mental deficiency is not a single entity but due to many factors, some of which may be prevented or controlled. They also suggest the hope that with adequate research, it may, someday, be possible to find those synthetic compounds which can be given to a defective child lacking the proper enzyme, thereby rescuing him from an incapacitating state. If this success can be repeated in other types of mental deficiency, we shall be more interested in identifying carriers and motivated to find preventive measures as well as corrective techniques. This will be increasingly true for the three dozen pathological states in the human which are at present thought to be of demonstrable human origin(1). While most of these occur infrequently (less than 1 in 10,000), the methods developed in studying them are of unknown but large potential benefit in our major diseases.

When we remember that the population of the world is now calculated to be about 2.5 billion and will probalby double in 58 years, it behooves us to follow these leads both for the sake of the immediate mastery of the conditions named and also for the probable gain *in methods* for studying behavioral patterns, both normal and disordered. I need not underscore the many additional pressures which will be a part of our own and our patients' problems due to the unavoidable stress imposed by such large populations.

Genetics is important in pointing out what is *not* hereditary, as well as in showing us what is. For example, the convulsive states are generally regarded as hereditary unless traumatic origins can be demonstrated. The evidence from family and encephalographic studies indicates it is one of the conditions in which a carrier state seems probable(2). Yet such experts in human genetics as Neel and Schull(3) are extremely cautious in their evaluation of the evidence and, in a grading system of 1 to 4 for reliability where 1 is most reliable, accord this evidence a slender 3. Kallmann cites his own uncertainties and those of others, in spite of the purported positive evidence, including the twin studies of Lennox and Solly. He also reports that Alstrom(4) "remained unconvinced of the statistical validity of these data. . . . In his opinion, only a small fraction of epileptics owe their disease to heredity." Among the numerous probable etiologic factors responsible for convulsive disorders we should not overlook those described by Freud in his essay on Dostoievsky and Parricide(5).

I am impressed by the rigorous discipline and careful workmanship of experimental geneticists in dealing with all their data, including the human. They accept the axiom that the adult is the result of interaction between the genetic factors and the environment at all stages of fertilization and development with a seriousness which gives us confidence that they can be of tremendous help to us in our search for causes and correctives in the more psychological disorders. This disciplined devotion to method has brought experimental geneticists to a careful experimental exploration of the operational meaning of "environment" in a manner which is most encouraging to a clinician. It seems to me that they will be most helpful to psychiatric theory in pointing out the pitfalls of either a misplaced belief in genetic control or an oversimplified environmentalism. Furthermore, geneticists and other workers in allied fields have pointed out the pitfalls in

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uncritical translation of animal experimentation (comparative genetics) to the human subject in view of the added complexities of the latter levels of organization. Sturtevant, Murphy, and Schnierla have described some of these fallacies in detail(6, 7, 8).

The older views of a gene as a golf ball, as an independent entity, with a simple pattern of one-to-one correspondence have been considerably revised. The concepts of polygenes, major genes, genic interaction, genic balance, environmentally contingent gene effects, phenocopies (a condition in which organisms which look alike actually prove to have different genetic heritage), and extranuclear reactions provide a more flexible model for explaining the manifold variations which are found in real life. The growth of critical skill in the light of more flexible concepts can be seen in the summary by Wright (1952) in regard to human intelligence studies (Colchester Studies by Penrose, 1938, Ohio Studies by Halperin (1945) for the lower grades and Terman (1925) and Hollingsworth (1940) for superior children).

In brief, while we recognize that quantitative variation in man has a genetic basis, we have made little progress toward sharply defining the genetic and nongenetic components of variation in particular cases [3, p. 114].

I believe that Dr. Kallmann's work deserves high praise for his comprehensive and enlightening series. The high standards developed by some geneticists, which may even lead to unfair criticism, may be seen in Neel and Schull's evaluation of human twin studies. They conclude (3, Chap. 16):

An objective evaluation of the contribution which twin studies have thus far made to human heredity is a matter of some complexity. That the studies have not made the contributions which Galton envisaged is certain. . . . But more important is the inherent difficulty in arriving at sound conclusions in the face of obscuring effects of the biological biases to which twin data are subject.

With improved background knowledge we can expect all psychiatrists who are also committed to the importance of genetic activity by means of instinct theories to be especially interested in the developments in genetics, ethnology (K. Lorenz, N. Tinbergen, E. Hess, J. P. Scott, J. Fuller, Wm. H. Thorpe), constitutional and cultural anthropology, social and experimental psychology, ecology, social psychiatry, in fact all those sciences which promise to give us a true experimental science of personality. Then we shall be able to work out in better detail the complexities of such concepts and hypotheses as the life and death instincts, the influence of heredity in (1) psychological expressions of sexuality including (2) allied forms of criminality, (3) the castration complex, (4) aggression, (5) guilt and similar concepts. It seems likely that such investigation will give us important data about ego structure, primary ego integrity, adaptivity, and the nature of the unconscious functions as Freud had predicted.

Although we cannot expect speedy progress in improving human population through eugenics programs, we can expect much more usable information through large surveys determining (1) existing pools of single genes, (2) the distribution of identifiable genes in the population, (3) the complex nature of inherited human behavioral patterns, and similar studies described by Dr. Muller. As he has told us, we shall then be able to identify and treat susceptible individuals and families with more accuracy and certainty.

George Gaylord Simpson(9) has pointed out the importance of an increasing inclination and ability "to think in terms of populations." We probably need much more description before we can do meaningful experiments, as pointed out by J. von Neumann last year at this meeting in his analysis of the auditory system. Although the study of the individual case is the approved clinical method, we must also study many cases with different methods and different observers in order to avoid the fallacies of a scientific myopia, and thus achieve a more comprehensive unified theory of psychiatry.

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DISCUSSION OF THE GENETICS SYMPOSIUM

BENTLEY GLASS, PH. D.,[1] BALTIMORE, MD.

To stress the alteration in the frequency of certain genes in the population which results from the modified rigor of natural selection brought about by our creation of an artificial environment and especially by the medical alleviation of illnesses once fatal at an early age, I might reinforce Dr. Muller's words with some of my own, written on a former occasion:

> By surrounding himself with a social environment, mankind has unwittingly modified the rigor of natural selection in many ways. The price we must pay, in the end, for the mercies of medical care and surgical aid is the dysgenic increase in the frequencies of certain detrimental genes whose effects we have learned to ameliorate. Thousands upon thousands of diabetics who in a former day would have died early in life are now saved by insulin to live relatively normal lives, and, of course, to pass on the gene responsible for their diabetes to their descendants. Myopia is no longer a grave handicap in life; hearing aids alleviate certain types of deafness. Probably no one would have it otherwise. Yet to contemplate a future population composed largely of persons who must wear both glasses and hearing aids, and must start the day by inserting their false teeth and taking first an insulin injection in one arm and then allergy shots in the other [and we might add, topping off their preparations for the day with a tranquillizing pill of some sort] is none too pleasant. To say the least, medical science is steadily increasing the load it must carry."

Dr. Pauling's lucid discussion of the ways in which genes influence and control the nature of hemoglobins and other biochemical substances which characterize the hereditary differences between people may be amplified so as to show how a knowledge of the existence and the exact position of a blocked metabolic step can lead to more illuminating experimental attacks on clinical problems. Dr. Pauling has described some of the earlier work with phenylketonuria, or phenylpyruvic oligophrenia, as it is also called. In this metabolic disorder, which is inherited as a simple recessive trait according to the pioneer studies of Fölling and of Jervis, the tissues are unable to convert the amino acid phenylalanine into tyrosine. Jervis has recently shown, by enzymatic studies of liver tissue from phenylketonuric individuals, that their tissues lack the enzymatic activity, readily demonstrable in the liver tissue of normal persons, for the conversion of phenylalanine to tyrosine. When a metabolic block of such a character occurs, the symptoms that result may arise from any or all of 3 causes: (1) the lack of the product normally formed, or of some of its subsequent secondary products; (2) the accumulation of the substrate, which is no longer transformed into the product; or (3) the production in enhanced amounts of toxic byproducts of the blocked substrate. In the case of phenylpyruvic oligophrenia, feeding patients with extra tyrosine does not alter the degree of mental deficiency, so that lack of the normal product is not a cause of the mental symptoms. British workers have lately reported that on the contrary keeping phenylketonuric patients on a diet very low in phenylalanine results in some cases in a noticeable improvement in their mental ability. Research may therefore now be directed to an investigation of the effects on the nervous system of phenylalanine itself or of byproducts produced from it, such as phenylpyruvic acid.

In spite of the biases inherent in the collection and interpretation of twin data, such studies can be invaluable in the investigation of chronic and mental diseases. The mere determination of the concordance and discordance between co-twins can be made much more valuable by collecting similar data for other degrees of relationship, such as full sibs, half-sibs, parents, step-sibs, spouses, and randomly selected control individuals, as Kallmann and Reisner did in their classic study of tuberculosis, and as Kallman has continued to do in his studies of the psychoses. Perhaps even more valuable, in the long run, are the uses to which co-twin material can be put in the study of norms and capacities of reaction. By alternately using one monozygous twin as subject and his co-twin as control, I have been able to demonstrate some very striking individual reactions to

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caffeine that are characteristic of particular genotypes. The possibilities can readily be extended to mental disease, as Lennox and Jolly have demonstrated in regard to the seizures, brain waves, and intelligence tests of epileptics. The "normal" monozygous twin of an epileptic and his affected co-twin constitute as good subjects as possible for the study of similarities in reaction capacity, such as the remarkable resemblance of their brain waves, and for obtaining insight into differences traceable to past experience and to external etiologic factors. Thus, so long as there is no brain damage, the IQ scores of monozygous twins remain extremely alike, whether both or only one of the twins has experienced seizures. But, once brain damage occurs in one twin, the intelligence scores of the co-twins assume a considerable difference. The experimental and continuous study of the monozygous twins of individuals with a chronic or a mental disease, together with the study of the heterozygous carriers of genes that in the homozygous condition produce pathologic effects, promises to become among the most significant ways in which the applications of genetics to disease can bring about fruitful results.

Thus population genetics, the analysis of hereditary biochemical differences, and co-twin experimentation alike emphasize the same conclusion. While the initiation of a chronic disease, and even of an infectious one, depends on some stress imposed by the environment on an individual beyond his capacity to resist, that very capacity to resist ultimately resides in the genes. In the future, physicians must take cognizance, if they are wise, of those hereditary differences that make it possible to predict that certain diseases will more probably appear in certain individuals, certain families, and certain races than in others, just as they recognize also that pathological symptoms will appear under certain external conditions more often than under others. If the physician is to treat the whole patient, and not work merely to efface the symptoms of disease, then genetic investigation is imperative. Genetics and biochemistry, advancing hand in hand, can pinpoint the critical defect, which then may be obviated. Nonetheless, in the long run the genetic welfare of the entire population must be balanced against the relief of the individual, for there is as yet no known cure for the sick gene itself. The genetic responsibility of the members of the psychiatric profession is thus exceedingly great.

LETTER FROM GERMANY

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In Western Germany psychiatric methods have undergone significant changes during the last 5 years. As in other countries, they especially concern drug therapy, which has been widely improved through the introduction of phenothiazines and alkaloids of Rauwolfia. This new trend can only be compared with the beginning of active psychiatric therapy in 1935 (shock therapy, etc.). To start with the standard methods:

Hardly anything has altered in the now classical insulin therapy (Sakel) during the last 10 years. All experienced authors recommend sufficiently long series and the creation of deep comas, lasting from half an hour to one hour. Of course, the technic of the treatment varies in the different hospitals. If the results are not yet quite satisfying, the reason might be found in a lack of technical organization rather than in the use of different technics. We think it is not advisable to treat the patients in the regular wards, where they are placed in accordance with their psychial and social behavior. We prefer the establishment of insulin pavillions. For this work we try to appoint only physicians who are not only well experienced in psychiatry but have a good knowledge of internal medicine as well. If the "insulin physician" changes to another place we see that his successor is made familiar with the technics of the treatment and the possibilities of complications before he takes over. Moreover, the insulin patients should be nursed by specially trained nurses and it should be possible to put them into single rooms, so as to be able to isolate agitated or extremely sensitive patients. We consider the arrangement of an insulin ward the best solution.

A remarkable therapeutic effect was noticed by Häfner(12). It is known that the insulin therapy causes an increase of weight in schizophrenic patients, a fact which was considered to be based specially on insulin. But it was interesting to see that our patients showed the same effect after electroconvulsive therapy. When Häfner went more deeply into the matter he stated that a certain change takes place in the bodily constitution with some of the cases. The direction of this characteristic change was always from the schizothymic leptosome to the cyclothyme pyknic type. Apparently the change of the constitutional character brought about a better resistance to psychosis, as it exists in the pyknic type even without any treatment. Patients who did not show any change of their constitution after treatment inclined more easily to new outbursts or deterioration of personality.

We still consider the acute infectious diseases such as active tuberculosis, diabetis mellitus, decompensated mitral and aortic insufficiency, and the more serious diseases of the liver as an absolute counterindication for insulin therapy. But there is no objection to using the method on patients with hypertonicities of the non-nephrogenic type.

Until 1935 the mortality of insulin therapy was between 1.3 and 1.6%. The degree of carefulness of technic plays an important part in the quota of mortality. The figures from our clinics lead to the conclusion that the mortality—if the treatment technic is corectly applied—does not exceed 1%, and can be lowered to less than 0.5% after better practical organization of the insulin wards.

Hibernation therapy in psychiatry is widely spread in Germany, since Laborit and Huguenard(18) first used derivatives of phenothiazin (Largactil) for accomplishing their *hibernation artificielle* in surgery (1948). We use these synthetic antihistamines, the derivatives of phenothiazine, Atosil, Latibon, Dibutil, Megaphen and others in combination(5, 12, 15, 24). These substances act strongly upon the vegetative system. It is supposed that they effect a chemical interruption of the fibers between the cerebral cortex and thalamus, a "pharmacologic lobotomy." Cases of schizophrenia which were already under treatment for several years and did not react to insulin,

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electroshock treatment, etc., showed an improvement after Megaphen treatment. The paranoid and catatonic subforms of schizophrenia also showed good results. It is easy to interrupt stupors and to calm exitation. About one-half of the paranoid schizophrenic patients showed a turn for the better, even when the treatment was stopped. The ability to make interpersonal contacts improved in hebephrenic and schizophrenic states, and mannerisms decreased. If the success is to be permanent, Megaphen must be given continually in an adequate dose. Patients with manic episodes show quicker results than after electroshock treatment, but not in all cases. The endogenous depressions could be toned down, the anxiously agitated responded better than the inhibited hypochrondriac forms. The patients were freer and lost their depressive thoughts and suicidal impulses. In the beginning of a depressive phase it is possible to give a certain relief to the patient from his agitated symptoms, easier than when using the older psychiatric methods. Megaphen combined with electroshock therapy some weeks after the beginning of depressive phases resulted in significant improvements.

In treating drug addicts, insulin in small doses is combined with Megaphen. The patients must reach a relaxed, sleepy state. Additional hypnotics are not required. By giving Megaphen in the evening for some time, sleep disturbances can be prevented.

There was good success in some cases of delirium tremens, which calmed down in 24 hours. The treatment lasts for about 3 weeks, but this depends entirely on the therapeutic effect. The hibernation treatment can be repeated if necesary. So far we have not made use of an additional supercooling, besides it would be too difficult to accomplish it with our patients. The hibernation treatment is far from being a panacea for mental diseases, but we think its results are more encouraging than the application of the other available drugs.

Concerning the undesired side-effects of this therapy H. J. Haase(9) described Parkinson syndromes after Megaphen (Lagactil)—therapy (1954). So far these treatment methods correspond with your own. A new development which has taken place in German psychiatry as well as in the treatment of organic diseases of the nervous system is a biological therapy. Its origin goes far back. In the 'twenties Plaut(23), then at the Kaiser Wilhelm Institute for Psychiatry in Munich, began careful experiments on the biology of brain substance. By these experiments he tried to find out whether lipoid antibodies of the brain, which we can identify *in vitro*, also play a part *in vivo*, if they come into contact with the living brain. It was remarkable that rabbits, preliminarily treated with brain substance, did not show any symptoms of sickness, although their serum contained brain autoantibodies. Even brain antisera of high efficiency, injected into the spinal canal, were perfectly compatible.

Especially this fact was important for certain therapeutic applications. Roeder(26) followed in the steps of Plaut and started to investigate the chemical structure and the metabolism of the different parts of the gray matter and topistic units of the brain stem, using isotopic methods. To put it briefly, some anatomically defined regions of the central nervous system possess a special chemical structure and metabolism. By this fact the posibility of a substitutional therapy for degenerative diseases of the central nervous system seemed to be given. Several cases of Parkinsonism were treated with injections of fresh substance of the corpus striatum of calves. Two or 3 days after the intramuscular injection the general habitus improved. Rigor and tremor decreased visibly, the patients felt relieved. This effect lasts for 4 weeks, then the injection must be repeated. We did not observe any anaphylactic or allergic reactions, just as Plaut did not find any while experimenting with his animals.

This effect seems to be specific in the constellation Parkinsonism-striatum-substance. No improvement was attained in a case of acute, quickly progressing spinal muscular atrophy by massive injections of anterior horn substance, motor bulbar nucleus and motor cerebral cortex. Biological methods of this type are beginning to be used for psychoses.

Here we must refer to the experiments of Kornmüller(16) although he started from quite another principle, suggested by the

work of Cerletti. First he injected into test animals extracts (lipoid solutions) of the brains of rabbits which had been subjected to several electroshocks. In the electroencephalogram the latter showed conditions as they are observed in the state after electroshock. This led to studying the effects of such extracts on psychoses. The extraction of these biocatalysts is done with acetone and ether. The effective extracts are left over, after the phosphatides have been precipitated. The observations of Kornmüller refer to manias, depressions, mixed psychoses, of the manic type mostly, and schizophrenia as well as psychopathy. The result was best with endogenous depressions. In extremely favorable cases the patients could be released already after several injections. But even in serious cases there was a close temporal connection between the injection and an astonishing improvement of the clinical state which lasted from 2 to 7 days. The injections immediately cause strong vegetative reactions, mostly well-defined deviations of pulse and blood pressure, especially lowering of the blood pressure. This is caused by the water-soluble ingredients of the brain extract. In the meantime it comes to symptoms of weariness which change over into shorter or longer sleep. The anxious restlessness is diminished, the patients feel quieter, become content, reveal their psychotic ideas and are more accessible to psychotherapy. Some patients who have experienced electroshock describe this state as similar to the awakening after this treatment.

The so-called delayed reaction which is caused by lipoid-soluble particles of the extracts appears on the first day after the injection, sometimes not before the second or third day. This mainly affects the rhythm of waking and sleeping, digestive function, and so on. The tormenting sleeplessness yields distinctly already in the following night, so that sleeping drugs, which were indispensable before, can be omitted. The appetite improves and persistent constipation stops, but the effects upon the central psychic functions, especially upon impulse and affectivity, are in the foreground. Already in the morning of the day following the injection many patients are distinctly more free and bright; their consciousness is less troubled by depressive contents. Sometimes we have observed deviations toward the manic side, but sometimes also a passing increase of depression. Whenever we asked the patients in this state how they were, we always heard that they felt more easy, quieter and more relaxed. They are especially relieved, when the painful organic feelings are decreasing. The effect of the injections passes a few days later. Then depressions combined with corresponding delusional ideas may start again. Sedative effects on patients, suffering from mania or mixed psychoses with mania dominating, were only short, lasting hardly longer than 2 days; a progressive improvement of the clinical picture could not be obtained. Contrasting with the good success in cases of depression the observations with schizophrenia were disappointing. While the biochemical catalyzers in the extracts of Kornmüller seem to have a direct effect on manic-depressive dementia, they do not influence diseases of the schizophrenic types.

In all cases which are not influenced by electroshock, insulin therapy, and other methods mentioned, we have started to use psychosurgical methods on a limited scale. In the clinic of Kötter in Braunschweig leukotomy is performed more frequently. It was here that Boehlke(1) developed a new method of leukotomy: The bisection of the brain substance is accomplished by the arched bending up of a steel wire, which is led through a hollow needle and can be erected by pressure. In this way the size of the cut can easily be calculated. The technical principle of this leukotome is similar to that of Nosik, who published it in May 1954.

Whether such a wide destruction of the fibres of the frontal lobe, as it has been practiced until now (when performing the standard methods) is really necessary seems doubtful to us! So we were led to use the stereo-encephalotomy (Spiegel, Wycis, Freed, Marks) as a psychosurgical method. Riechert(25) started it on a bigger scale in the neurosurgical clinic in Freiburg. The author introduced it in Göttingen, where it is used on therapy resistant psychotics. We observed good effects after the bilateral coagulation of the medial nucleus of the thalamus, especially a decrease of the nervous ten-

sion, restlessness, and hallucinations. Some of our worst showed a very marked improvement shortly after this operation. Instead of being aggressive, tense, and negativistic, they were managable, cooperative and were able to start with occupational therapy. From being introverted and autistic, they became extraverted and liberated from their specific schizophrenic attitude. If hallucinations remained, they ceased to produce their inner mental effects. The unwanted side-effects of the prefrontal lobotomy did not occur. The success with obsessive neurosis was excellent. The gyrus rectus of the orbital frontal brain was interrupted on 2 or 3 points on the subdominant side. By this method a decrease of pathologic impulse is gained with encouraging results. These aimed divisions of the cerebral tracts are called "hodotomy" (13) (the interruption of a tract, a pathway). On our way to achieve more subtle methods of treating psychoses we were inspired by the work of Papez and McLean on the limbic system, especially its anterior temporal portion. Morbid processes in these structures seem to be not only basically concerned in the pathogenesis of psychomotor epilepsy, but also in that of mental diseases, as especially the papers of Freeman and Williams on the relations of auditory hallucinations to the amygdaloid nucleus have shown. But the system we are specially interested in (from the operative point of view) is the anterior cerebral pole and the medial nuclei of the thalamus, which belong to the lastest developed systems of the frontal brain. But many observations will be necessary before the foundations of these operative interventions will become more exact.

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NEUROPHYSIOLOGIC AND PHARMACOLOGIC INFLUENCES ON EXPERIMENTAL NEUROSES [1]

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As do humans, the lower animals differ widely in their capacity to adapt to configurations of stress and conflict. This paper reports an analysis of various biodynamic and environmental factors in the susceptibility of cats and monkeys to the induction of experimental neuroses and to subsequent therapy.

METHODS

Subjects.—There were 142 cats ranging in age from 6 months to adulthood and 43 monkeys (2 African vervets, 5 African mangabeys, 7 South American spider monkeys and the rest rhesus) from about 1 to 20 years old.

Training and Observation.—All animals were trained to discriminate visual, auditory, temporal, and other cues and to respond to them by pressing the appropriate one of two levers the required number of times for a reward from a designated food box. The period required for maximal performance averaged from 2 to 6 months in the cat and from 3 to 8 months in the monkey; however, some animals were studied for 2 years before other experimental procedures were begun. During this interval observations were made in both laboratory and living quarters as to each animal's metabolic processes and activity under varying circumstances, its sexual and exploratory patterns, its social behavior with cage and colony mates, and its relationships to other species including the experimenters. These observations were rated on 30 6-point scales previously demonstrated to possess high reliability.

Drug Studies.—The effects of alcohol, barbiturates, opiates, lysergic acid, mephenesin, dexamyl, dibenzyline, reserpine, Thorazine, and Miltown were studied on groups of 10 to 30 cats and monkeys. These drugs were administered in capsule or in food, by gastric tube or by parenteral injection, the technique of administration optimally effective and least disturbing to the animal being the one of choice. Dosages ranged from those producing no apparent changes to maximal sublethal effects. Each drug was used from 10 to 60 or more times per animal, and its effects in normal animals were compared with those induced in animals which had been rendered experimentally neurotic or had been subjected to various cerebral lesions.

Production of Experimental Neuroses.—As described in previous reports, neuroses were induced in our animals by exposing them to adaptational conflicts between learned patterns for securing food (or, in the monkey, a tendency to persist in learned food-seeking even in the absence of a direct hunger drive) as opposed to fear of the repetition of a threatening experience. In the cat, effective deterrents were a mild grille shock, an air blast, or, in 3 cases, the loss of dominance in group competition. Those used with the monkey were grille shock, a jet of water, or, more significantly, the sudden appearance of a toy rubber snake in the food box. From 10 to 50 such experiential traumata presented irregularly at the time of food-taking produced in a few days or weeks marked and persistent deviations of behavior characterized by physiologic manifestations of severe anxiety and somatic malfunctions, generalized phobias and compulsions, disruption of learned patterns, sexual and social aberrations and, in some monkeys, evidences of hallucinated or delusional behavior. All of these patterns were rated on appropriate 6-point scales and many were recorded on motion picture film for later comparisons. The animals were then further observed for spontaneous developments in their neurotic be-

[1] Read at the 112th annual meeting of The American Psychiatric Association, Chicago, Ill., April 30-May 4, 1956. Aided by Grant M-730 from the United States Public Health Service, Contract DA-49-007-MD-403 with the Office of the Surgeon General and a grant from the Mental Health Fund of the Department of Public Welfare of the State of Illinois.

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havior or, as previously described, were treated by various techniques including brain surgery.

Cerebral Lesions.—Twenty-two normal monkeys and 27 normal cats and 18 neurotic monkeys and 23 neurotic cats were subjected to bilateral surgical lesions in cingulate areas 23 and 24, orbitofrontal area 13 and the amygdaloid nuclei or to stereotaxic destruction of the mediodorsal or anterior thalamic nuclei. These animals were further observed for from 8 to 36 months before anatomical control studies were made of the site and extent of the cerebral lesions.

In 16 monkeys which showed almost complete diminution of previous neurotic symptomatology through brain surgery and other therapy, a second neurosis was induced.

Methods of Analysis

Since, in general, the variables which influenced resistance to the induction of neuroses and subsequent recovery were found to be similar in monkeys and cats except in regard to the effect of drugs, only the data on monkeys need be presented and analyzed here.

CATEGORIES OF DATA

These were rated on 5-point or other appropriate scales as follows:

Age.—Our 43 monkeys were divided [8] into 2 groups, one of 13 animals estimated to be younger than 3 years and the rest older. This was done because the 2 populations, as will be demonstrated, differed significantly in their spontaneous behavior and in their responses to experimental procedures.

Adaptation to Laboratory Routine.—This category was derived from highly reliable ratings of (1) the time required to teach the animal to enter the transport cages willingly; (2) manifestations of fear or anger toward the experimenters; (3) the number of days before the monkey would eat food freely available in the experimental apparatus; (4) resistance to the initiation of learning (avoidance of levers, etc.); and (5) the consistency of these patterns.

Learning.—This was derived from the learning scores of the monkeys on several problems, requiring counting, switch manipulation, and spatial discrimination. However, the ratings do not isolate the learning capacity of the animal since this is also influenced by factors of motivation, adaptation ($r = .546$) and other variables.

Resistance to Induction of Neuroses.—Twenty-three of the 43 monkeys employed characteristic adaptive maneuvers during the induction of neuroses, ranging from sitting immobile in the apparatus while observed by the experimenter, switching hands or reaching with the mouth to secure food, snatching or throwing the food, appealing to one or another experimenter, etc. These maneuvers were rated as to number and duration.

Spacing of Traumata.—The conflict-engendering experiences were repeated at a rate of from 1 or 2 daily to 3 or 4 over a 3-week period and were rated according to the intervening intervals, from 1 for those administered close together to 5 when they were widely spaced.

Number of Traumata.—Ratings were also made of the number of traumatic stimuli required to induce nearly maximal neurotic patterns, 1 for less than 5 traumata to 5 for more than 25.

Time for Induction of Neurosis.—Similarly, the period necesary for reaching the near maximal neurotic symptomatology was rated as 1 for 2 weeks or less up to 5 for more than 5 weeks.

Course of Recovery.—This was indicated by the reduction of specific, highly reliable ratings of various neurotic symptoms, ranging from 1 for a reduction of less than 1 point to 5 for a reduction of between 4 and 5 points in 4 months.

TREATMENT OF THE DATA

Wherever possible product-moment correlations were calculated, although our data do not meet all of the assumptions implicit in the mathematical models on which this statistic is based. Nevertheless, despite the relatively small numbers and the many interactions, most of these correlations are statistically significant; further, the consistency of

[8] Where there was difficulty in doing this, the size of the animal, the conformation of its teeth and its rate of growth during its stay in the laboratory were used as indices.

TABLE 1

INFLUENCE OF AGE ON OTHER VARIABLES
(Under 3 years—13; over 3 years—30)

	A Adaptation to laboratory routine		B Learning		C Substitutive maneuvers	
	− 3 %	3 + %	− 3 %	3 + %	− 3 %	3 + %
1	14.5	13.3	30.8	6.7	46.1	46.6
2	29.0	40.0	23.0	13.3	30.8	16.7
3	23.0	16.6	30.8	46.6	15.4	13.3
4	14.5	6.7	15.4	20.0	7.7	13.3
5	14.5	23.2	0.0	13.3	0.0	10.0

	D Number of trauma		E Time for induction		F Progress of recovery	
	− 3 %	3 + %	− 3 %	3 + %	− 3 %	3 + %
1	38.5	10.0	23.1	0.0	38.5	0.0
2	15.4	23.3	53.8	10.0	46.4	10.0
3	30.8	30.0	23.1	46.6	7.7	36.6
4	15.4	26.6	0.0	33.3	7.7	30.0
5	0.0	10.0	0.0	10.0	0.0	23.3

the trends indicates that they are hardly likely to be the result of chance. Ideally the interactions would be partialled out, but the data are not reliable enough or sufficiently numerous to justify this procedure. Similarly, we have avoided setting up the usual confidence limits as these relationships should be regarded only as good estimates.

Those variables for which product-moment correlations could not be obtained and which could not meet the assumptions behind r_{bis} and r_{tet} are presented in the form of percentage tables. However, the trend of the data is again apparent.

RESULTS

Age.—As indicated in box A of Table 1, there is little difference between our 2 age groups in regard to adaptation to laboratory procedures, although it should be noted that the 4 most adaptable young animals were spiders and mangabeys which tend to make better initial adjustments than does the rhesus. However, it can be seen in B that the older animals tend to be better learners than the younger. Similarly sub-table C shows that, while almost half of our animals employed no definitely classifiable substitutive maneuvers during neurotigenesis, the older ones were much more likely to do so than their younger mates. Corresponding comparisons in D indicate a definite tendency for the younger animals to show full neurotic symptomatology after fewer traumata. This vulnerability is even more apparent in the time required to induce a neurosis and in the ratings under F for limitation of recovery.

Adaptation to Laboratory Routine.—The data presented in Table 2 under the column labeled Adaptation indicate a moderate but consistent positive relationship between general adaptability to laboratory routine and resistance to neurosis as well as to subsequent rapidity of recovery.

Learning.—This column indicates a moderately high correlation between speed and effectiveness of learning and temporal resistance to neurosis. However, there was only

TABLE 2

PRODUCT-MOMENT CORRELATIONS AMONG VARIABLES

	Adaptation	Learning	Spacing of traumata	Substitutive maneuvers
Adaptation to laboratory routine	—	.546	—	.624
Learning	.546	—	—	.472
Number of traumata to produce neurosis	.266	.216	−.815	.475
Time required to produce neurosis	.433	.631	.032	.445
Progress of recovery	.423	.470	.025	.364

a low relationship with the number of traumata required to induce neurosis and a moderate correlation with rate of recovery.

Spacing of Traumata.—This column shows a high negative relationship in line 3 indicating that if the conflictful experiences are relatively widely spaced, they are more neurotigenic; however, the time actually required to induce neurotic responses or to effect recovery was not significantly affected because others variables were also involved.

Substitutive Maneuvers.—As is evident in column 4, animals which had adapted and learned well were more apt to use substitutive maneuvers in protecting themselves against conflict, and were also likely to recover from neuroses more quickly.

Nature of Traumata.—No relationship between the severity of the neurosis and the nature of the trauma—rubber snake, grille shock, or a combination of these—is demonstrable in our data except where less effective stimuli such as streams of air or water were used. However, 4 animals which were only mildly affected by grille shock were very disturbed by exposure to the toy snake.

Nature of Surroundings.—Twelve monkeys were subjected to conflictual traumata in an experimental cage that permitted partial escape to narrow ledges or across a barrier whereas the remaining group of 31 were made neurotic in an apparatus that allowed no such opportunities. The constricted monkeys had a mean scale rating of 2.55 for number of traumata required as compared with a mean of 3.4 for the others, while the corresponding means for time required were 2.9 and 3.3. In effect, room for psychological as well as physical distancing from the site of a conflict diminished its neurotigenic effects.

Species.—Two vervet monkeys showed the greatest resistance to conflict whereas our spiders and mangabeys, despite excellent adaptive capacities, proved to have the least resistance of all the animals to the induction of neurosis (mean ratings of 2.1 as to number of traumata required and 2.8 as to time necessary as compared with means of 3.1 and 3.2 for the rest of the group). This difference did not hold for progress of recovery.

Brain Lesions.—The ratings in Table 3 show that monkeys with brain lesions are somewhat less resistant to the induction of neurosis; the ratings being .4 of a point lower in number of traumata required and .8 point in time necessary for induction. There is also .4 of a point difference in progress of recovery. With the exception of 2 animals with lesions in cingulate area 24 which had high ratings, the location of the lesion made only a small difference in their resistance to stress. The data for animals made neurotic a second time were similar to those cited.

Drugs.—All but 2 of the younger monkeys were studied for the effects of one or more drugs either during the induction or in the course of their neuroses. In moderate dosage, with the possible exception of alcohol, no drug protected the animal from the effects of stress.

Likewise, while barbiturates, alcohol, and some of the ataraxic drugs administered to cats during retraining or other therapeutic procedures sometimes slightly ameliorated neurotic symptomatology, there were no persistently favorable effects in the monkeys.

TABLE 3

THE DISTRIBUTIONS IN ROUNDED PERCENTAGES ON SCALES FOR INDUCTION OF AND RECOVERY FROM NEUROSIS IN MONKEYS WITH AND WITHOUT BRAIN LESIONS

	Number of traumata		Time of induction		Progress of recovery	
	With lesion %	Without lesion %	With lesion %	Without lesion %	With lesion %	Without lesion %
1	22.5	9.5	9.0	4.8	13.5	9.5
2	13.5	23.7	22.5	4.8	22.5	19.0
3	36.0	23.7	45.0	47.5	31.5	23.7
4	22.5	32.5	13.5	38.0	22.5	23.7
5	4.5	9.5	9.0	4.8	9.0	23.7
Mean rating	2.7	3.1	2.5	3.3	2.9	3.3

RÉSUMÉ

A differential analysis of observations on 142 cats and 43 monkeys during the last 12 years indicates that animals which adapted well to general laboratory routine, which learned efficiently, and which explored various substitutive maneuvers in initial efforts to resolve conflictful situations, subsequently showed longer continued resistance to severe stress and resumed effective behavior more readily under therapy. Younger animals were more susceptible to the induction of neurosis than were older ones and there were definite species differences: *i.e.* spider monkeys and mangabeys were more vulnerable to conflict than were vervets and rhesus. Other factors which expedited neurotigenesis were: repetition of the traumatic experiences at unexpectedly long intervals, minimal opportunities to escape from traumata, representational reenforcement (*e.g.* rubber snake with grille shock added) and a diminution of adaptive capacities produced by cerebral lesions.

Our data indicate that better adaptability and more efficient learning (correlated at $r = .546$) represent in part a greater capacity to perceive and remember and integrate, thus for a time making possible a broader versatility of adaptive and substitutive responses before eventual breakdown occurs. Conversely, young animals which have only partially developed these abilities or brain-damaged animals which have partially lost them can deal less adequately with continued stress and conflict and therefore more readily develop patterns sufficiently persistent, generalized, and disruptive to be termed neurotic.

Finally, it is evident that behavioral phenomena even when directly observed and partially isolated in the laboratory must always be viewed against a rich context of interactions among the innate capacities and acquired patterns of the animal as continually modified by its constantly changing evaluations of and transactions with its environment.

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THERAPEUTIC RESULTS IN MENTAL HOSPITALS WITH A MINIMUM OF PROFESSIONAL PERSONNEL [1]

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Some patients in public mental hospitals improve sufficiently to return to their families and their occupations without having received any medication or psychiatric treatment. There are others whose illnesses are modified to such an extent that the slight amount of treatment they receive seems insufficient to account for the favorable changes that take place. Some illnesses, like reactive depressions, toxic confusional states and the acute reactions induced by the withdrawal of alcohol and certain drugs, are known to be self-limited. The recovery of patients who are hospitalized because of these conditions can be predicted and the factors that effect recovery would also seem to be understandable. In addition to these, there are other patients who improve, without benefit of treatment, from such illnesses as severe and prolonged anxiety, exacerbations of schizophrenic illnesses, addiction to demerol, and the involutional depressions. The recovery of some patients from these illnesses without adequate custodial care and without psychiatric treatment is unexpected and unusual. It cannot be regarded as spontaneous because it always occurs during the period of hospitalization and is always attributed to the hospital by the patients and their families. Like many other recoveries from mental illnesses, the details of the recovery process are lacking.

Psychiatrists, like other physicians, are motivated to relieve suffering. When they succeed they rightfully feel that they have fulfilled their responsibility. They have not yet been trained to see that it is as important to understand the psychological factors that effect recovery from mental illness as it is to understand the remote and the recent events which brought it about. No intensive, detailed study of the total recovery process of patients who were hospitalized because of their mental illnesses has been reported. It would seem imperative that clinical investigation of this sort be undertaken with patients in mental hospitals who are not receiving specific psychiatric treatment. Continuing observations of these patients might also clarify the extraneous factors that impede recovery. Information regarding all the nonpsychiatric influences that assist in bringing about improvement from mental disorders might also prove useful for the future care of patients in mental hospitals.

At the present time it is difficult to estimate the optimum improvement of some patients in relation to their discharge from hospital care. Some patients show a steadily increasing improvement from the time of their admission. This may be observed within the first 10 days or the first fortnight. If they do not leave the hospital then, and they usually do not, because psychiatrists do not trust early improvements, these patients then appear to lose what progress they have made and again become as ill as at the time of their admission. It would be worthwhile to learn as much as possible about these initial improvements by encouraging a selected number of patients to leave the hospital at such times to test the strength of what gains they have made and to continue their treatment on an ambulatory basis.

The lack of accurate knowledge about the psychological factors that influence improvement or recovery from mental illnesses in hospitalized patients is related categorically to the evaluation of the quality of improvement when decisions regarding the discharge of patients need to be made. In one public hospital, for example, on an occasion when beds were urgently needed for the admission of a number of acutely ill patients, no beds were available. The professional staff reluctantly discharged patients whom they regarded as not having recovered enough to return to their families as well as others about whom they were highly doubtful. All of the patients whom they discharged, with few ex-

[1] Read in the Section on Mental Hospitals at the 112th annual meeting of The American Psychiatric Association, Chicago, Ill., April 30-May 4, 1956.

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ceptions, were able to continue to live in the communities where they had previously resided.

Many psychiatrists can recall isolated instances of recovery in hospital of patients who had not received any treatment. They can also describe specific events which they thought were related to the improvements which these patients manifested. These events, however, were not usually observed during the time they occurred but were ascribed to the improvements somewhat later.

In some mental hospitals which have a somewhat adequate number of psychiatric residents and in which some of the patients undergo individual psychotherapy by psychiatrists-in-training there is more opportunity to observe what benefits accrue from psychotherapy and what other day-to-day experiences are of value in assisting patients' recoveries. Those who supervise the residents in their therapy with patients have the obligation to help them maintain a continuing awareness of the major influences effecting improvements that are not apparently connected with the psychotherapy as well as any benefit that patients derive from their psychiatric treatment. The commonly observed tendency to overevaluate psychotherapy is thereby protected, and the residents have opportunity to investigate all the factors effecting recovery.

A married man was readmitted to a hospital for treatment of addiction to demerol. The hospital record showed that he had been previously diagnosed as a sociopathic personality with drug addiction. His life history was that of a person who had never had the kind of father he needed and he had developed one relationship after another with older men with whom he worked and could admire for their achievements and who in turn cared about him. These relationships eventually terminated, and after the patient became increasingly successful in his own right as an electronics engineer he developed a painful illness. During this illness his treatment included injections of demerol. After his recovery his need for demerol continued and this was the beginning of his addiction. His first mental hospitalization was terminated by the patient himself and was of short duration. During his second admission he entered into psychotherapy with a member of the resident staff and, despite frequent interviews, it was evident that he was lacking in his motivation to get well. During this time, however, it happened that he no longer felt any need for demerol. He had discontinued the use of the drug and, what was equally amazing, he experienced no symptoms from its withdrawal. The patient did not know how this change had taken place, but, as he said, he was certain that it had not resulted from the psychotherapy. The therapist was equally inclined to this belief. The patient's improvement remained an enigma until it was learned from someone other than the patient that he had exchanged his so-called addiction for the close relationship he had developed with an older man who was also a patient in the hospital. He had referred to this older patient only occasionally in his therapeutic interviews and then only briefly. It was also learned that the patient did not spend an unusual amount of time with the older man but the satisfaction he derived from this father relationship continued after he left the hospital and has sustained him ever since. He has again become productive in his work, has no need for any drug, and says that he feels better than he has for years.

This thumb-nail sketch is naturally devoid of many important details and leaves many questions unanswered. It does, however, indicate the principal factor in at least the transitory recovery of a patient during his hospitalization which would otherwise have remained unclear. It likewise throws considerable light on the prognosis and the need for plans to assist this patient in the future.

A middle-aged woman came into psychotherapy in the outpatient department of a mental hospital. She was suffering from persistent and severe anxiety, had lost much weight, had attempted suicide on 2 occasions, and had developed fleeting delusions about her neighbors. After intensive efforts at psychotherapy combined with sedation had failed she finally was persuaded to be admitted to the hospital. During the first several days after admission the same psychiatric resident who had worked with her so unsuccessfully in the outpatient department continued to visit with her but only briefly. She was given no medication. Within 5 days this very sick patient began to eat heartily, to sleep soundly, and she visited freely with other patients and said she was entirely well. She had been observed by the psychiatric residents, by the nurses, and the psychiatric aides and no one, including the patient herself, could offer any explanation for her dramatic recovery. She begged to return to her home because she felt so well and she saw no reason to remain. She was willing, however, to follow advice and she continued in the hospital for an additional 3 weeks. During this period she was engaged in almost daily interviews in an effort to learn what factors had led to her recovery. The only significant fact uncovered was her repeated assertion that she had regained her health because she felt accepted and at-one with the other patients in the hospital. Her statement was regarded as significant because she had been estranged from her parents and her siblings for several years and always re-

fused to have anything to do with her neighbors whom she believed to be jealous of her attractive appearance, her pretty clothes, etc. Nothing beyond what the patient herself had said about her improvement was ever learned. It was enough, however, to suggest the possibility that her hospitalization and her identification with other patients was a reinstatement of her relationship with her brothers and sisters during an early period of her life. Before leaving the hospital she spoke of starting her life over again, of the mistake she had made in not being friendly with her family and her neighbors. After returning home she appeared to remain well for a few weeks but then gradually became ill again. Before her symptoms became as severe as they had been previously she entered into psychotherapy with a psychiatrist in private practice.

These brief descriptions of transitory recoveries of patients in 2 different mental hospitals, which were achieved apparently without benefit of psychiatric treatment but were clearly dependent upon psychiatric hospitalization, are included for the purpose of emphasizing that which seems important at this period in the further development of psychiatry. In our preoccupation and intensive striving to staff our public hospitals with adequate numbers of professional personnel, so sorely needed, we ought also to be mindful of the fact that even in those institutions which have a minimum of psychiatrists, nurses, social workers, and aides, there are always some patients who find their own ways of recovery and return to their families and their jobs. Their improvements may be no more than temporary but they do represent surcease from suffering. They may take place in the most unattractive and uncomfortable surroundings or in the best equipped and most modern hospital. We do not know the number of patients who are benefited principally by having been hospitalized and what significance the hospitalization has for them. We do not know how frequently the influence of another patient, or group of patients, or nurse, or psychiatric aide, or adequate custodial care, has effected favorable modifications of mental illness. We are inclined to think of a combination of wholesome influences rather than any single hospital relationship or other experience. Until we have more accurate data, however, we know this aspect of our daily work insufficiently well.

The need for evaluating psychotherapy is ever before us and the efforts which are being made to accomplish this are encouraging, indeed. In mental hospitals with almost adequate numbers of competent professional personnel there is opportunity for carefully conducted studies of the total recovery process. This will, naturally, need to be limited to those patients whose treatment is limited to psychotherapy, or to those patients who begin to show improvement and who receive no specific psychiatric treatment. These tasks do not represent new proposals. They are outlined to emphasize what is well known but which needs to be presented again and again.

DISCUSSION

ADDISON M. DUVAL, M. D. (Washington, D. C.). —Spontaneous recovery is a term rather frequently used to describe the successful rehabilitation of hospitalized mentally ill patients who have been given no specific psychiatric therapy. This is a dubious term at best and probably indicates lack of specific knowledge concerning the reasons for the patient's improvement. I am more inclined to attribute this improvement to such things as the climate of the hospital, the relationships of the patient to ward and staff personnel, to general attitudes, such as interest in the patient, kindliness, and tolerance, as well as to the impact on the patient of proper treatment facilities including hospital architecture. I believe these things can have an enormous impact on the patient for good and they often help him to mobilize his own natural inclinations toward normalcy. Sometimes the shock of seeing so many patients "worse off" than he results in a patient's gaining renewed courage and determination.

The present need for careful evaluation of the hospital climate has resulted in our turning to the sociologist for assistance not only in providing new knowledge but in providing interpretations for the benefit of our patients. This newer knowledge is permitting us to "structure" the hospital climate in various ways which are not yet fully clear or complete. Also, the trend toward patient participation in general treatment programs, with researches into patient influence on patient is a fascinating new field of exploration. At our hospital (Saint Elizabeths, in Washington) we are daring to follow some of these changing concepts. For instance, we are now mixing the sexes in activity groups on the ward—both for therapy and recreation—where heretofore such mixing was permitted only in off-the-ward recreation or conference rooms. We are trying a plan to abolish "disturbed wards" and "suicidal wards" through the development of patient participation in which a group of patients will help assume the responsibility for looking after a special patient who might be classed as disturbed or suicidal. A crisis situation may develop with our

first successful suicide in this type of climate. It is hoped that the hospital administration will not be forced from this type of patient-participation plan by possible resulting community pressures and demands after such a suicide, including increased protective and security features such as were in vogue before these new treatment ideas developed. Our hospital is now being sued for negligence because we permitted a patient, who had been suicidal but then improved, to have a bathrobe with attached belt of like material, with which she successfully hung herself to a window. Most of us would agree, I am sure, that the hospital which never has a suicide is really not a hospital but the public (and the courts) need to be educated to this idea. Our defense in this suit is embodied in the simple statement that the providing of a bathrobe is but one of the essentials of humane treatment and that we would be negligent if we did not provide such essentials.

THE PROBLEM OF AMBULATORY SCHIZOPHRENIAS [1]

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The history of psychiatry quite often shows certain characteristics of general, or political, or economic history, or even of the history of science. This is not surprising, since psychiatric history is as much a history of human beings as any other history, and therefore is bound to share with all other histories the weaknesses, particularly the proneness to commit errors, common to all men. However, during the past 350 years we seem to have learned to be more tolerant with regard to scientific errors. In matters concerning politics or religion we are still quick to condemn errors, and to combat the mistaken views and those who entertain them as if we were dealing with a more or less criminal or immoral act, and a willful one to boot.

Psychiatry, as a discipline, ever since it was differentiated from dogmatic theology as well as pathological anatomy—and this liberation took place gradually, becoming a visible fact only very recently—does rightfully claim a definite position in the hierarchy of medical disciplines. It also insists that it is close, and must remain quite close, to sociology and anthropology and the humanities in general—as much as medicine must keep a close working relationship with physiology and chemistry. It is this close relationship of psychiatry to the humanities, and the problems of values and of various modalities of human actions, that makes the weaknesses and errors which are found in the history of psychiatry appear more glaring. These errors arouse in us such discontent and passionate impatience that some of us become harsh and intolerant, and others glib and insensitive to clinical detail.

All of us are subject to the widespread weakness of terminological emphasis, *i.e.* catchwords. In no other aspect of psychiatry do these impediments to scientific and clinical clarity appear more prominent than in discussions of the problem of schizophrenias. Many still consider the term "schizophrenia" a mere substitute for the term "dementia praecox"; so many, while using the Bleulerian term, still view a schizophrenic from the standpoint of the Kraepelinian principle of prognosis. Schizophrenia, in this respect, appears only a modern catchword which does not relieve us of the older diagnostic-prognostic fatalism which the term dementia praecox conveys. That Bleuler, in changing the clinical designation, also emphasized that the affectivity in what used to be called dementia praecox is never lost and that the amenability to treatment ("good prognosis") ought never to be excluded in these conditions, is recalled by comparatively few among us.

Some psychoanalysts, the majority I would say, shy away from treating schizophrenias because schizophrenias, like the older *dementia praecox*, appear to them not amenable to treatment at all. Other psychoanalysts, these are a very small minority, find that schizophrenias *are* amenable to psychotherapy. Regardless of the efforts required and the great difficulties encountered, these psychoanalysts stand their ground as hopeful pioneers whose hopes are really justified more often than not—provided tolerance and patience are blended with scientific perseverance and the psychological endurance of the therapist.

When I speak of the therapy of schizophrenias I deliberately leave out of consideration the variety of shock and surgical and pharmacological therapies. These are of a totally different order and are of little concern in a discussion of the issues involved in the clinical psychology of schizophrenias. In other words, I am concerned here only with psychopathology and psychotherapy. And because it is psychopathology that is my concern I find myself in a rather junglelike nook in which the flora is rich and thick but the perspective rather nonexistent. To clear a passageway in this jungle is not easy. I shall limit myself to the statement that such

[1] Read at the 112th annual meeting of The American Psychiatric Association, Chicago, Ill., Apr. 30-May 4, 1956.

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a passageway is not yet at hand, and that I find it impossible at this juncture to undertake the job of making one myself; perhaps this is the reason why I want to limit myself to the easier task of pointing out only certain errors.

I have mentioned catchwords and alluded to their perseverant power in our clinical thought. Take as an instance the excellent work on pseudoneurotic schizophrenias by Hoch and Polatin(1), and some of the supplementary commentaries made by Axel(2). Hoch and Polatin quite obviously have in mind a number of cases which I ventured to call ambulatory schizophrenias(3) some years ago. Their interest in schizophrenias is expressed in the fully modern terms with which contemporary psychology, under the influence of psychoanalysis, has made us familiar; they speak of free associations, for instance, and of anxiety. Yet they show the tendency toward neologisms ("pan-anxiety") which is almost always a sign of clinical uncertainty; and at the same time they seem to be affected by the older, pre-Freudian and pre-Bleulerian tradition of the nontreatable nature of the condition. Even the term "pseudoneurotic schizophrenia" seems to suggest that in terms of purely descriptive emphasis on symptoms one could differentiate between a neurosis which promises a good prognosis, and a psychosis (schizophrenia) which promises the opposite. In other words the older Kraepelinian, rather nonpersonal or nonindividualistic, formal attitude keeps coming to the surface despite the apparent and honest effort to remain among the ranks of contemporaries.

Again, in the discussion of which Axel's contribution is rather typical, we find a general modern psychodynamic orientation, yet the older mannerisms of the older psychiatry come to the surface when a purely verbal and actually nonexistent difference between autistic and dereistic thinking is discussed, despite the fact (which seems to be overlooked in this paper) that Bleuler himself merely suggested that "dereistic" would seem to him a better term, even though he meant it to mean the same thing as "autistic."

Yet despite this unclarity of clinical perspective, and despite a considerable confusion which appears of semantic nature but rather indicates that we are impressed with catchwords into which we continue to pour the meaning of older catchwords—despite all this, there seems to be a general feeling if not an overt agreement that neuroses and psychoses are sharply delineated clinical entities; that sharp delineations are found only in formal textbooks of psychiatry and in the jargon which is neither scientific nor clinical-empirical, and that "intermediate" forms do exist; that so-called compulsion neuroses, particularly the severe ones, are at times hardly distinguishable from moderate, or even moderately severe, schizophrenias.

It would be difficult, very difficult in my opinion, to pin our hopes on this type of thinking as the distinguishing feature of schizophrenias, for here again that typical disturbance in thinking which Bleuler described originally as characteristic of schizophrenias, is not easily demonstrated clinically. The reason is that only in advanced phases of schizophrenia does that which Bleuler called *primary* disorder come fully to the surface. Ordinarily the clinical picture is dominated by the symptomatology which Bleuler called *secondary*, and which on the whole represents the clinical picture originally sketched by Kraepelin. During the past 45 years our knowledge of the working of the unconscious has broadened and deepened to a very great extent. Our technique of evaluating the *meaning* of the ideational content of our patients has become considerably refined. Consequently, both Bleuler's formulations and Kraepelin's descriptions have acquired a meaning.

What I have just said is to be emphatically noted; for the tradition of catchwords in which we are always involved has led the majority, if not all, of us to the misconception that Bleuler may have been terminologically right but Kraepelin was wrong from the outset, and that the so-called newer, dynamic psychiatry required a complete revision of the older, erroneous one. That this is not true, historically as well as psychologically, has been stated many times. This contention between "the-old-to-be-discarded" and "the-new-to-be-inaugurated" is another example of how catchwords and slogans affect our psychiatric thinking, actually impeding our development.

As I myself have stated many times, Kraepelin, Freud, and Bleuler were actual contemporaries. Kraepelin was born in the same year as Freud, and Bleuler was but 1 year younger. All 3 lived to a ripe old age, and they all completed their respective scientific tasks more or less fully before they died. I, for one, am unable to see that there was an actual struggle, still less a battle, between the allegedly old and the allegedly new in the clinical work of Kraepelin, Bleuler, and Freud. Rather, I see in Kraepelin the completion of the task of clinical psychiatric observations, in Bleuler the infusion of these observations with the ideational and affective content, and in Freud illumination of this ideational and affective content—all 3 contributions, historically speaking, proceeding simultaneously and fulfilling the task which the nineteenth century had assigned to psychiatry with considerable impetus.

Were it not for World War II and the demand for quick therapeutic results no matter what, I believe we would have escaped to a very great extent the confusion in present-day psychiatry which is due to the tenacious adherence to catchwords and slogans. However, no period of history escapes its share of slavish adherence to certain catchwords; or, to put it differently, no historical period attains complete independence from the domain of tradition. If such independence could by a miracle be achieved, it would be truly fatal. For such an independence would be able to look only into the future, and anything that has no past has no future either.

The simultaneous fulfillment of the historical psychiatric trend with which the nineteenth century closed is nowhere reflected more poignantly than in a certain type of discussion which of recent years seems to have become frequent, more presistent in all walks of clinical psychopathology. The American Psychoanalytic Society has repeatedly put on its annual program the discussion of so-called borderline cases; in certain psychiatric circles the pseudoneurotic schizophrenias are brought forth—a group of cases which at least in part, and probably fully, would fall under the heading of so-called borderline cases or, as I prefer to call them, ambulatory schizophrenias.

We must be clear at least on one point: whatever label you pin on these cases, they seem to be cases of some transitional or intermediary type which do not fit into Kraepelin's classification without reservation. They do not fit the Bleulerian descriptions as understood by us and, without being able to admit it, we still cling to Kraepelin because he seems to have been the only one who offered a classification that appealed to our sense of order and simplicity. Nor do these cases fit the so-called Freudian mechanisms because psychoanalysis, as should have been expected, never was able to create a psychiatry of its own—that is to say, a psychiatric nosology independent of Kraepelin and Bleuler. Freud himself was not a well-trained psychiatrist, and even if he had been his task was only the clinical understanding of the unconscious content of patients. No independent nosology was required for this purpose; the purpose could be achieved without any nosology whatsoever.

Hence the recent concentration of interest on so-called borderline cases. Whatever the theoretical discussions, gyrations, and point-stretching one might engage in on this score, the fact that remains clear is this: there is a psychiatric area of theoretical penumbra, called by some "borderline," in which there reigns considerable chaos or confusion with regard to clinical criteria and diagnostic differentiation. In this area the clinical psychiatrist who adheres to descriptive nosology feels free to use newer concepts and terminology and yet fails to clarify the confusion of the borderland; in the same area the psychoanalyst feels free to use some of the traditional nosological criteria, and yet fails to clarify the chaos of the penumbra.

This conclusion may at first glance appear disappointing and quite discouraging, but in actuality it is a disappointment only insofar as we always strive for orderliness and systematization; whenever clinical data fail to fit into our man-made order or system, we feel keenly disappointed. Then, or often, we quite unwittingly begin to pull our observations by the bootstraps, as it were, in order to fit them into our preconceived order or system. This is what has happened, I believe, in psychiatry and in psychoanalysis during the course of the past quarter of a century or

so. Having increased the acuity of our clinical observations and the depth of our psychological understanding, we quite naturally, quite inevitably, came upon a series of psychopathological phenomena which was neither the thing we used to think it was, nor the thing we thought it ought to be, nor the thing it might get to be.

In the late 'twenties psychoanalysis came upon such a series of psychopathological syndromes, which it was unable to call by any of the names to which it was accustomed; it was not even able to find any of the traditional symptoms in those cases. Yet there was no doubt in the clinician's mind that they were real "cases," so to speak. A descriptive term was then introduced—"a-symptomatic neuroses," or "neurotic characters." Later on the severer forms of these neurotic characters, or character neuroses, began to be called "psychopathic personalities," or "psychopaths." In the course of recent years we have been witnessing a renewed search for some nosological clarification of these phenomena, which undoubtedly had been manifesting themselves under our own eyes for many years but had remained unnoticed, or improperly observed, until the ever-increasing refinement of our psychological insight and clinical intuition made the observation of these phenomena inescapable. I, for one, have no doubt that the ambulatory schizophrenias belong to this group of clinical problems which of recent years began to present themselves to our clinical eye clearly yet without any specific nosological face.

From the practical point of view, it really matters little what nosological pigeonhole we might find for these cases; nor does it matter whether they belong to the neurotic group with the theoretically good prognosis, or to the psychotic group with the theoretically bad prognosis. What does matter is that the clinical condition in question would not have come to the serious attention of the psychotherapist some 20 or 25 years ago. It would have been noticed by the members of the family; it would have been given by them that universal diagnosis which is called "being very difficult," and would have been given that conditionally bad prognosis, addressed to the would-be patient: "If-you-don't-get-a-hold-of-yourself you are-in-for-trouble."

Today, whatever psychiatric appellation we might prefer for such cases, we really do not have to wait for the trouble in years to come. We see the trouble right here and now, and we proceed with the work of psychotherapeutic influence. This psychotherapeutic optimism we owe primarily to Eugen Bleuler. It was he who opened the prison gates as it were; one is tempted to say that in this respect Bleuler's optimism as to the possibilities for the recovery of schizophrenias presents as great a service to psychiatry as the liberation of the mentally ill in France carried out by Philippe Pinel some 120 years before.

It is not possible here to give any hard and fast rules as to what technical devices are indicated in the psychotherapy of such cases. The cases of ambulatory schizophrenias present an unusual variety of symptoms and reactions. The words of the late Thomas W. Salmon come to mind. He used to recall that someone referred to syphilis as the experimental laboratory for clinical medicine, because syphilis at its different stages is able to reproduce almost any type of illness known to clinical medicine. Likewise, Salmon used to say, schizophrenia might be considered the experimental laboratory of clinical psychopathology.

For this reason I feel reluctant to accept without serious reservations the term "pseudoneurotic schizophrenia"—for after all schizophrenia remains the fundamental "experiment" as it were, in a given case. Therefore, the presence of so-called neurotic symptoms should not disconcert us in schizophrenias, any more than alcoholism, with its many sequelae, should be considered as a possible mask for schizophrenia. (As a matter of fact, Bleuler rightly maintained that psychopathological complications of alcoholism which show hallucinosis should not be considered alcoholic hallucinoses but schizophrenias with severe alcoholism.)

We may therefore safely state that the ambulatory schizophrenias, regardless of the particular type of symptomatology and, I must say, regardless of their apparent inability to do free associations, *are* amenable to psychotherapy. And, I should add, they

are amenable to psychotherapy much more than is generally assumed.

These schizophrenics have an inordinate capacity to attach themselves to the therapist, almost as much as they have of sharply breaking away from the therapist and slipping into a kind of wordless, autistic state. Even while in this seemingly irreversible autistic state, they are open to considerable psychotherapeutic influences.

I knew of an 18-year-old girl whose presenting symptoms were inability to get on with her schoolwork, and a tendency to become "abstracted." She would look off in a semisomnolent manner as if completely oblivious of her surroundings, or of time, or of what there was for her to do, seemingly impervious to any appeals "to wake up" and to pay some attention to what was being told her. When she walked, her movements were swift and energetic, but rather devoid of purpose; thus, on her way to the doctor's office, she would wander on "to take a walk" and would never arrive to see her doctor at all that day. She would not telephone to say that she was not coming, or that she was sorry she had missed the appointment. She was quite disorderly about her appearance. She would set her watch 1 hour ahead so as not to be late, and yet would come an hour late because her watch had stopped (this with a smile), either because she had forgotten to wind it or because "it must have gotten wet" when she took a bath and forgot to take it off. She would go for rather long periods without taking a bath. She would walk in the streets or parks for hours, sometimes throughout the night, oblivious of the rain or cold despite her being dressed rather lightly. She would lock herself in her room and cry for hours without apparent reason. She would play records throughout the night or, again, cover the record player and the telephone with a couple of pillows and blankets so as "not to be disturbed" and then go to sleep without undressing. She always carried several books under her arm and wore a vacuous smile on her face, was almost always disheveled, and quite uncommunicative. She would eat immense amounts of food for weeks, and then stop and pretty nearly starve herself for short periods. She would give as reasons for her behavior merely that she felt bored, or sad, or "not very happy"—that was all.

At times the clinical picture was that of an advanced schizophrenia showing considerable intellectual deterioration. When she did speak, she spoke in generalities and abstractions which one was unable to grasp at all—a typical dereistic type of verbigeration rather than communicative talk.

The patient's attitude toward her father and mother, sisters and brothers was verbally solicitous, kind, and even friendly; yet this attitude alternated swiftly and often with tearful impatience "for no reason whatsoever," and with explosive, tantrum-like hostility. She would establish very quick, clinging friendships with women of her own, or mainly her own, age and just as invariably would turn against them, unable to bear them in a manner of mute rage. In other words, it was very difficult indeed to find a companion who would be helpful to her even without exercising any supervisory authority over her. As to young men, she seemed to be either totally unaware of them, or distant, cold, and consciously rather indifferent to them.

As to her sexual feelings, she honestly claimed that she had none and never had experienced any in the past. She seemed to talk about sex with equanimity and frankness, yet with total absence of curiosity and apparently obvious boredom. She did not appear to dissemble, but she really did seem unaware of any reactions toward men or of men's attitudes toward her. As a matter of fact, I was astonished to find that with a cool, straight face and a monotonous, kind of bored surprise at the skeptical look that I must have betrayed, she disclaimed any knowledge as to what sexual life is all about. She seemed quite sincere when she asserted that she knew nothing about autoerotic practices and had no idea of what the actual relationship between the sexes is. This particular ignorance, as we shall see, soon proved quite revealing, for the apparent ignorance served as a cover for many experiences and much imagery which were at the time totally repressed.

This phenomenon is not an infrequent finding in schizophrenias. It is idle to bring up now the perennial discussion as to the strength of the superego or the weakness of the ego in schizophrenics. Whether we decide that the ego of schizophrenics is too weak to assimilate their sexual drives, or that their superego is too strong in asserting itself and in forcing the schizophrenics to repress their sexuality, the clinical result is the same: at first sight, we seem to deal with the total repression of sexuality. I am inclined to favor the opinion that it is the superego that is hypertrophied and overwhelms the more or less usual, if not normally strong, ego.

The reason for my predilection is this: ever since I first came upon the finding(4) that at the bottom of the young schizophrenic reaction lies a complete suppression of sexuality, imposed from the outside on the child who is the future schizophrenic, I became inclined to the belief that a powerful and cruel superego imposes its demand on the ego to such a violent extent that the ego, whatever its relative strength, is overwhelmed and the consequent impression that we deal with a very weak one is gained. There is still another reason why I am in-

clined to favor this view. It is precisely because the ego of some, or of many, schizophrenics is sufficient unto the person we happen to be dealing with that some psychotherapeutic successes could be achieved in these cases. The therapist is of course unable to create an ego *de novo*. The biopsychological core of the ego is too well established at the time the psychosis develops, at the age of 18, 20, 30, or 40. However, what *is* within the power of the psychotherapist is to affect the pathological influence of the superego, or the effect of the pathological superego, which is the same thing. The superego being the result of incorporated objects external to the person, it could be modified to a great extent by skillful psychotherapeutic influences insofar as the patient ultimately develops an identification with (the incorporation of) the therapist, abandoning in part or even to a great extent earlier identifications which were saturated with paralyzing hostility and swings into extremes because of ambivalence.

As I have said before, the patient of whom I have sketched a surface clinical picture belonged to the type whose sexuality had been deeply buried since early childhood. During the first months of her treatment her intense dependence on her mother began to show itself as being in great part a covered-up, intense resentment of her mother and of all those who had taken her mother's place from the patient's childhood till puberty. The patient gradually recalled—at first with the characteristic schizophrenic calm, then with violent resentment—how her mother would look at the little girl's finger, then smell it—evenings when putting her to bed and mornings when getting her out of bed—and how the little girl would get frightened when her mother would "catch the scent" of her daughter's infantile masturbation and without much ado or explanation would spank her into infantile purity. After recalling these early childhood punishments, the patient began to show mild ideas of reference: people were looking at her in the street and perhaps making remarks about her—she knew not what exactly, but there was something sexual about those remarks. Thus she gradually became aware of her own sexuality, first by way of projections, then gradually by becoming aware of her own sexual feelings and interests. It turned out that she had always known "all about it" but dared not to know what she knew.

In order to complete the clinical picture, may I note merely by way of mention that there came into evidence a considerable admixture of unconscious homosexuality; it was this highly disguised homosexuality that seemed to be responsible for the extreme polarity of her relationship to girls of her own age and to somewhat older women.

There was also a characteristic set of symptoms which were related to a special form of acting out and exhibitionism, the real goal and meaning of which remained unconscious of course, but at the beginning only; for hours she would act in front of a mirror reciting Shakespearean and other roles. She loved this occupation; she would engage in it with abandon, even with ecstasy—although when with others she would be taciturn, tongue-tied, self-conscious to the point of tears. But in front of the mirror, alone with herself, she would pose, grimace, dress up, undress while reciting, and this gave her a sense of joy and of accomplishment.

On one or two occasions she developed a friendship with a passive man who asked for nothing and remained respectfully friendly, a pleasant onlooker. She would then suddenly conceive the idea of driving through the night into a neighboring town—she was a sort of tireless, restless person—then, doing actually nothing in particular but remaining on the move. She would run out into the garden barefooted, dancing cheerfully in the light of the moon, and on several occasions got fully undressed, covered herself with an Indian sari, and stretched herself out on an oriental rug—all this while completely unaware of the role of deliberate seducer which she was playing before a man who just looked at her. She was so fully unaware of her sexual play that, had the man made the slightest move toward her, she would have been horrified at his impertinence. She chose her men well, as you see. When the possible nature of her acting was pointed out, she merely asked in a tone of mild surprise and amusement and incredulity: "Really—do you really think so?" It was some months before she fully appreciated the nature of her behavior, recaptured her true sexual feeling and became transformed into a very well-measured and charming, socially very agreeable person. Again, she arrived at this level via ideas of reference and a suspicious attitude toward men.

The finer details of the structure of this girl's psychic apparatus, of the transformation of her feminine narcissism into a more simple, almost housewifely, interest in the various members of her family and even in cooking and mending, will not be gone into here. What matters here is the extraordinary flexibility, even elasticity, of these schizophrenics and consequently the great promise they represent from the psychotherapeutic point of view.

The secret of this success does not lie in any specialized technique. The latter must be psychoanalytically oriented, of course, and the psychotherapist must frequently be far from passive. At times he must be not only perseverant but insistent. He must avoid too logical, too intellectual interpretations, for this is one of the most dangerous pitfalls in the treatment of schizophrenics; it is easy to use the intellectual components as a springboard for abstract gyrations, indulgence in generalities, and those discussions of general principles which leave out everything personal and throw the patient back into verbal autism.

From the outset, and for a long time during the treatment which lasted over 4 years, the patient liked music, philosophical books, abstract paintings, general poetical vagaries, but she would actually be unable to remember what she had had for luncheon or when she got up on a given morning. It is the constant testing of reality that must occupy the therapist and at times in the therapeutic hour it seems more important to pin the patient down as to what particular vegetable was served at dinner time, or what this or that woman wore for tea, than to find out at the moment why or about what the patient happened to cry or to be angry.

I am inclined to emphasize this aspect in the therapy of ambulatory schizophrenias, because the so-called "total push" of Myerson, or "direct analysis" of Rosen, would be of little avail in these cases. For what is remarkable in these cases is their terrible passivity; they are prone to "fold up" and "give in" under the slightest pressure. They are difficult cases, but they are different from the well-defined, more or less advanced, crystallized schizophrenias of various types. They seem to be more or less undifferentiated, or not sufficiently defined so to speak, and they bear many earmarks of many potential schizophrenic entities, running the whole scale from the schizophrenia simplex to the expansive, florid type.

In other words, they are early schizophrenias which we learn to diagnose, as such, much earlier in the course of the illness than we did some 30 years ago.

Consequently, as I said in the beginning, I would prefer to preserve the term "ambulatory schizophrenias" rather than "borderline cases" or "pseudoneurotic schizophrenias," in order to emphasize the need for the development of ever greater diagnostic acumen, and ever greater knowledge of the psychotherapeutic possibilities. I am afraid that other designations convey a somewhat undecided attitude to both aspects of the problem, at least from the clincial, didactic point of view, and drive us unbeknown to ourselves into that state of mind which recognizes only the very well defined, *i.e.*, the well advanced and the established.

We must never forget that what Freud said about hallucinations holds true also of the other well-established symptoms: they are the result of a long process which went on for a long time before, and these are pathological attempts at recovery and pathological restitution of lost reality. Once this process of "restitution" is far advanced, the therapy becomes more difficult and the hopes for a good result more doubtful. It is the ambulatory schizophrenic who still "ambles" along in the world of reality that can be saved, regardless of his apparently tenacious clinging to his pathological adjustment.

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ANXIETY PROBLEMS WITHIN CULTURAL SETTINGS[1]

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Behavior in the human being can scarcely be conceived, much less understood, without considering the cultural context. Forces from without (nurture) stimulate the organism as do forces from within (nature), and both modify and pattern the personality(1).

The individual tries to acquire material which the environment refuses to give; on the other hand, the environment, society, or culture tries to force material that the individual tries to reject. Neuroses are thus frustrated goal-directed (motivated) activities representing noneffective "adaptation to stress and conflict"(2). If the individual cannot cope with the conflict, anxiety defense mechanisms develop.

There may be indicated 3 types of anxiety: ego, id, super-ego anxiety. For example, ego anxiety might be thought to exist in the man who exhibits typical symptoms toward the beginning of the end of his working career. Restlessness, tension, apprehension, sleeplessness, loss of appetite appear apparently without reason. Investigation shows that a junior is moving up, with energy and judgment, and the threat of displacement is in the offing—the physiology and unconscious mind can react to the situation before the conscious self recognizes and evaluates it. This is becoming more and more a cultural anxiety in our society. Medicine has prolonged life, and maintained physical and intellectual vigor beyond the traditional years. Yet concepts from outmoded medicine and out-dated ideas of industrial usefulness are creating new cultural, "mental," and economic problems—conflicts and anxieties which our society has not yet learned to solve. Premature retirement, a sort of Cultural Alzheimer's Anxiety, is a new condition which calls for new psycho-socio-economic solutions.

Instinctive or id anxiety might be illustrated by the persistent, handicapping apprehension of the stenographer whose elevator got stuck in a burning building; or, the man whose parents died when he was under 6 years of age, who was shifted to relatives, whose older sisters finally reared him without male influence, and who had many illnesses in growing up, chiefly of a respiratory sort. He had a sort of permanent fund of anxiety or lowered resistance in his personality. To stresses, whether of an economic, professional, or business nature, he had an anxious set which might be called instinctive anxiety. His physical or mental state can not be properly evaluated from time to time nor treated adequately without considering the cultural as well as the medical condition through which he has lived.

Superego anxiety is the background of many unidentified tensions and unspecific somatic disorders. It is related to the general atmosphere of the aggressive, competing, struggling, aspiring U.S.A. of the twentieth century. Can I succeed? Can I survive? Will I attain prestige, power, success, things, status, comfort? Will I outdo myself, my parents, and the Joneses? Can I keep my head above water with the energy and effort it entails? The level of aspiration and drain is pretty strenuous. The fear of failure, of falling, of submersion, dependency, humiliation, and extinction *is* a cultural phenomenon which may be involved in any headache, palpitation, indigestion, insomnia. The aspirations, goals, standards, values of a society determine, among other things, muscle tensions and illness.

This is the cultural setting of much disease. Halliday, a number of years ago, pointed out that the indices of psycho-social illness are rising: infertility rate, peptic ulcer, suicide, exophthalmic goiter, diabetes, and hypertension(3). Lawrence Frank writes on *Society as the Patient*(4).

Superego anxiety exists at times in professional men in religion, the clergy, and the priests. They are supposed to live by more than human standards. It may arise in the cultural setting of the man brought up with

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a sensitive, conservative, conscientious, clerical background, involved in a broker's business inherited from the other side of the family. Realistic necessities in this area of cultural values and modes may paralyze the nepotist, as we have not infrequently seen.

Anxiety has different origins according to competent thinkers. Anxiety and fear perhaps are evolved from the "startle reflex" as described by Landis and Hunt(5). According to Goldstein, anxiety is the experience of the organism in a catastrophic condition. For Freud anxiety is the threat of break-through of erotic or aggressive impulses and perceived as a danger signal. The symptoms and inhibitions are developed to avoid anxiety. Rank, Adler, Jung, Alexander, Horney, Fromm, Kardiner, Sullivan pointed to anxiety orgins in the trauma of birth and separations, inadequacies and inferiorities, the break-through of the irrational, hostility and aggression, helplessness, isolation, taboos blocking the child's relaxation or pleasure patterns, social and self-disapproval. Mowrer's theory is that fear of social punishment, withdrawal of love and approval are repressed, and that the associated fears and guilt repressed become neurotic anxiety. Thus he developed a guilt theory of anxiety as opposed to an impulse theory. To complete this array of assumptions, the existentialists from Kierkegaard to Tillich speak of anxiety as being involved in actualizing any possibility, in creativity, the realization of self-hood, of the inevitability of anxiety, its confrontation in the development of individuation; freedom and responsibility as goals of personality, and anxiety as inherent in the possibility of freedom. Anxiety is the reaction to the threat of non-being, to the threat of meaninglessness in one's existence. The capacity to bear anxiety is a measure of selfhood.

The profusion of diversity and conflict of theories is enough to cause a kind of cultural anxiety among psychiatrists and analysts themselves. It might almost seem that they create anxiety to cure it. There are, furthermore, cultural conflicts and anxieties among psychiatrists, psychoanalysts, and social workers, and among different schools of analysis. There are professional castration threats that reinforce indoctrination and membership in certain groups. Anxiety exists in the cultural relations of psychiatrists, psychologists, and psychoanalysts, in a kind and proportion that does not exist among biological scientists and practitioners of medicine. There is not a Boston and Philadelphia anemia but there are different types of psychiatry and analysis in different cities of the country. No wonder the public is often confused. There are historic and legitimate reasons for some of this which could be interpreted to the public. But the variety of formulations certainly does not warrant the dogmatism that exists in some thinking. The variety indicates a heuristic richness which can stimulate investigation and research and offer a variety of tools for the alleviation of disorders of personality.

What relevance does all this have to anxiety within cultures? We are beginning to study with profit the culture of the hospital community where the different goals of the various groups of personnel may conflict to the detriment of the patient. Reflection on the state of psychiatric thinking and training indicates that the cultural homeostasis in psychiatry is under considerable strain and that it might be profitable to study more objectively the cultural climate of our own discipline with the concept of university education in mind.

Cultural conflicts and tensions are not confined to psychiatry. Other branches of medicine are showing cultural changes. There is the cultural contrast between those who tend to stick to the structural, the anatomic, the physiologic and pathologic and pharmacological and those who are stressing the social aspects and functions of medicine. The public is becoming increasingly involved and concerned in this conflict.

Cultures as customs, beliefs, practices, and expectations are conditions of experience as well as physiology and structure. They modify not only ideas but feelings, preferences, physiology, and behavior.

Cultural attitudes influence human growth and development. One of my patient's earliest memories was of crying, pain, and hunger. Her pediatrician belonged to the obsessive self-confident culture that controlled physiology and feeding by rules and edicts opposing the humanitarian cultural

feelings of the mother. She deferred to authority. The patient remains in middle life subject to hunger pains and continual doctoring. Indigestion, pain, hunger remain, only the crying has changed; it appears in stomach disturbances and reinforces them.

Parents of extreme Prussian culture impressed their rigid rules of performance and cleanliness on eliminative processes too early. Duty was the word for defecation. The strands and straps of constriction were drawn so tight that only a psychosis of hate, symbolic destructiveness, and appeasement could and did finally break the parental hold.

Cross cultural contacts may be the source of anxiety and psychosis. A girl brought up in the isolation of wealth and snobbishness could not marry a man who "worked" because a gentleman does not work. Biological and social frustration developed pressures issuing in psychosis where only in phantasy, revery, and delusion could her natural urges be fulfilled and released from the domination of parental culture. Another girl burst similar bonds of isolation and overprotection in a reversal of training by dashing into unconventionality and promiscuity.

Conflict of religion and economic culture is not infrequent. A man was brought up under strong maternal and religious influence. Kindness, fair play, deference were virtues cultivated in him. When his college friends carried him into competitive business, he collapsed because he did not have the aggressiveness to compete and survive. It took 5 years for him to catch his breath, reorganize his resources, and take his part in society as a contributing member.

A man and a woman showed similar problems. Both grew up in the tradition of large families—the children looking after the parents in their ageing. Their children, much fewer in number, came into contact with the active hurrying, independent, achieving culture of thriving, alive America. Individualism was accentuated. Parents were left alone except for financial contributions. Both the man's and the woman's frustrations and hostilities moved into self-disappointment, self-dissatisfaction, self-castigation—or melancholia.

The overprotection and overdirection of a pietistic, religious culture, closely knit, did not prepare a gentle, young girl for her contact with a lively spontaneous, wholesome extraverted group in another city. Her feeling of difference was accentuated into delusions of reference and persecution. She had illusions on looking into a mirror of seeing herself as a howling hyena with horrible fangs. Ten years of psychotherapy were required to help her rescind her hostilities and distortions and move into friendly relations with for her a new and distant culture.

An extreme case of cultural constriction was a 33-year-old woman brought up in an extraordinarily pietistic sect in the mid-west. The cultural and familial rigidities, taboos, and phobias sound almost unbelievable. Work was to be her life. Only boy-crazy girls went to high school. She was told not to speak to boys and men except the few relatives who visited the family. She was hired out as a family helper and was warned against any but the most formal contacts with the male members of the household. Recreation, amusement, socialization were taboo. "I get tired and feel exhausted. Sometimes it takes my appetite and sleep. I am trying to keep from becoming too mentally depressed. Have been fighting a losing battle for years." Why she was not severely depressed or psychotic was difficult to understand. Her anxieties seemed to be reactions to cultural pressures rather than to intrapsychic echoes of childhood traumata. There had been a continued struggle against external conditions. She always maintained a bite on reality and finally, with support from her therapist, was able to shake herself loose from sick reality and move constructively into a new, more wholesome reality. One is sometimes tempted to enter deep psychotherapy fascinated by intriguing patterns in psychopathology. By moving in on a comparatively direct plan of reinforcing and guiding constructive impulses she was salvaged both mentally and vocationally. She was advised to move hundreds of miles from her home and culture—to Philadelphia, where she took a practical nursing course and established herself on her own, developed satisfying social and recreational activities with religious affiliations of a less extreme form. Therapy can often be appropriate and effective only if it considers the external cultural and environmental attitudes and relationships.

Anthropology brings to attention the relativity of culture—rules, regulations, customs, beliefs, expectations, taboos, rewards, acceptances, punishment. The Balinese woman wears no clothing above the waist. In America technically such behavior violates the mores. However, fashion makes certain accommodations between extremes of instinct and restriction, a certain suggestive approach to the Balinese is found unofficially interesting and attractive to a significant portion of the population.

The relativity of culture could bring to mind the relativity of concepts and formulations in psychiatry. Unfortunately, so often one finds in this profession the protectiveness of absolutes and controlling conformities, which one thinks of as signs of immaturity in patients.

Among the Marquesans there is little breast feeding and it is believed this tends to make the children anxious and insecure. In the Alorese there is absence of genuine security and affection of the mother for the child; the adult appears as rather disorganized with much submerged hostility. This is in contrast to the Navahos who, being accepted and loved as children, develop secure and confident personalities(6).

Halliday points out the increase in obsessiveness in western cultures. He believes this is related to repressive child rearing in infancy. Carothers speaks of the rarity of psychoses among preliterates. Among the Debuans paranoid conditions are culturally dominant(7).

In our culture manics seem to be decreasing. Carothers in Africa believes manics far outnumber depressions. Hysteria has changed its manifestations greatly since the times of Charcot and the early days of Freud. It has been said that the ratio of obsessive conditions to hysterical was greater in the last World War than in the first. Psychoneurotic reactions decreased during the stringencies of German war camps. Faris and Dunham believed that schizophrenia came chiefly from slum areas, while manic-depressives came from upper levels. Redlich studied the incidence of psychoses and neuroses in different socio-economic classes in New Haven. The incidence of psychoses increased as the socio-economic scale decreased, while the incidence of neuroses diminished. Methods of therapy show a cultural distribution—psychoanalysis is used by the upper economic classes; physical methods more by the lower economic brackets. Psychoanalysis is much more prevalent in American psychiatric thinking and practice than in England, France, or present-day Germany. It is not used in totalitarian countries.

Margaret Mead(8) notes that anthropology can throw "light upon an understanding of human psychodynamics, check tendencies to read our own special local social forms into theories, and broaden our views of the many potentialities which each human being has for constructing viable ways of life" (p. 420). And finally the goals of psychiatry and anthropology have something in common in "constructing, out of our insights, cultures in which human potentialities will have fuller play" (p. 433). Viewing the formulations, concepts, and theories of psychiatry and psychoanalysis in the broader perspectives of anthropology will help us develop sharper outlines and deepen our insights. Perhaps too we will be able to overlook some of our parochial perspectives, eliminate some of our defensiveness and hostilities, and join in a collaborative *eros* or *agape* for the benefit of our patients and the survival of mankind.

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THE ATARACTIC DRUGS: THE PRESENT POSITION OF CHLORPROMAZINE, FRENQUEL, PACATAL, AND RESERPINE IN THE PSYCHIATRIC HOSPITAL [1, 2]

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The desire to take medicine is perhaps the greatest feature which distinguishes man from animals.
SIR WILLIAM OSLER(1)

Perhaps never before in the field of emotional conflict have so many medicines been consumed by so many patients with so many diverse results as in the psychiatric hospitals of North America during the past 2 years that have seen the birth of the ataractic era. It has been a painful period of parturition for those of us who are reluctant to reformulate our psychiatric concepts at the sensationalistic behest of ill-advised and overoptimistic publications. Some enthusiastic members of our own fraternity have not been completely free from criticism in this respect. I have attended conferences on these drugs where the atmosphere approached that of a revivalist meeting.

Chlorpromazine and reserpine have been advocated for the treatment of every condition from anxiety to zoophobia. No wonder that there is chaos in this field, with many psychiatrists doubting what are the real indications for these drugs and, perhaps, pondering their own inability to confirm the optimistic claims advanced by research workers whom they trust, admire, and respect.

We have all heard so many panegyrics on these drugs individually that an attempt at their collective appraisal might help to clarify the present position. In giving you an account of our own experiences with these ataraxics, I hope to act as a purveyor of ataraxy itself and that, in medical terminology, means "freedom from confusion and anxiety." In my Oxford dictionary it is defined as "stoic indifference"—you may need that as well!

We have a small modern veterans psychiatric unit of 550 beds; 200 for senile and failing psychotics and 350 for the admission and active treatment cases. During the past 5 years we have had just over 1,100 admissions (31% return cases) and over 1,000 dicharges. We have only a small staff of 8 psychiatrists, half of whom are still in training. However, we receive many of our admissions directly from the armed services shortly after their symptoms develop and, in addition, we offer rehabilitation services, including job-replacement, outpatient support, and financial aid to many of our discharged patients, for, with commendable foresight, our Canadian cousins have given pensions only to psychotics, whom they help, and not to neurotics, whom they hinder. I think that this eulogy of our psychiatric facilities is important in the objective assessment of what these new drugs will do and will not do. Here is no static, custodial backwater in which the administration of new drugs to a mass of patients might draw attention to the overlooked fact that many of them had spontaneously improved during the years.

In this optimistic and busy setting we started using chlorpromazine over 2 years ago. We were early in this field as we were fortunate in having Dr. Hanrahan, who, with Dr. Lehmann(2), did the original North American research on chlorpromazine, as a frequent visitor to our staff conferences and his experience and advice were of considerable help in starting our work with this new drug. Our results were so encouraging that we started to use reserpine as soon as it became available.

Now, what did we learn from these 2 drugs? First, that in chlorpromazine we had, for the first time, a drug that would

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tranquillize without stupefying. It was more effective than electrotherapy in aborting manic attacks and could replace much of the maintenance electroconvulsive therapy which we had been using extensively to prevent the regression of chronic schizophrenics. It was also much more effective than any sedatives we had in the symptomatic control of excitement, aggression, destructiveness, and restlessness. Given in conjunction with ECT it shortened the course of treatment and either prevented the postconvulsive confusion frequently encountered after long courses of treatment, or, if it did develop, helped its resolution.

This reduction in the number of electric treatments and the confusion usually accompanying them enabled us to shorten the patient's hospitalization by applying supportive psychotherapy, with emphasis on complete honesty and the reality situation, at a date earlier in the acute psychoses than would formerly have been possible. We did not find chlorpromazine to be as good a tranquillizing agent as reserpine in the elderly patients because of the development of orthostatic hypotension, confusion, and mild pyrexia.

In treating schizophrenics we were able to confirm Kline's(3) findings of a period of sedation followed by turbulence and reintegration with large doses of reserpine, and we used this method of treatment in acute psychoses showing withdrawal and apathy. We reserved chlorpromazine for the agitated schizophrenic but found that often ECT had to be used as well before the patient became amenable to psychotherapy.

Emboldened by these findings we discontinued insulin coma therapy on July 1, 1955, and substituted intensive group therapy using chlorpromazine and reserpine as adjuvants. This new project rejoiced in the singularly cacaphonous designation of "The Ataraxic Push Group"—but it worked.

Personally, I have long regarded insulin merely as an adjuvant to group psychotherapy, but it is a messy form of treatment, expensive, time-consuming, and, with a 0.6% mortality rate and prolonged comas, it is frequently shock therapy not only for the patients but for the staff as well. So I was strongly motivated for the change.

At the beginning of the "Ataraxic Push Group" the nurses were quite resentful of their altered role and, at first, the patients were also. Many patients sat around with the wooden expression of the early stages of Parkinsonism, with pieces of tissue stuffed into their mouths to absorb the saliva—reserpine has such aesthetically unpleasant side-effects—or restlessly tottered around the room in a state of emotional turbulence. However, they did become amenable to psychotherapy and the physician in charge of the group, who has had considerable experience with insulin, is firmly convinced that this is a better form of treatment. His very enthusiasm must have made a significant contribution to the success of the project.

Let me give you some figures. In 1954, 26 patients received insulin coma therapy with a 90% remission rate, in the last 6 months of 1955, 30 patients were treated in the ataraxic group—all have been discharged from hospital and are fully employed and adjusting satisfactorily.

The modifications we have learned from experience are that there is no need to have the unpleasant side-effects mentioned earlier. We have gradually used reserpine less and less and replaced it with chlorpromazine. The Parkinsonian symptoms that still occur are controlled by Cogentin. The indication for inclusion in this group has also changed. At first it was merely a continuation of insulin coma group. Now we can include patients whose physical condition would have contraindicated that form of treatment and those schizophrenics who fail to respond to supportive psychotherapy given in conjunction with ECT or ataraxics or both.

There are 3 small, closed, side-room sections that used to be filled to overflowing with disturbed patients requiring isolation. Five years ago, with the aid of ECT, I was able to empty one of these sections and use it as a probation ward. Last July, we decided to do something about the hard core of disturbed and aggressive patients who still haunted the remaining 2 sections and to attempt to reintegrate these 15 rugged individualists into the large wards.

With the help of large doses of chlorpromazine and reserpine we were soon able to reduce them to a state of benevolent

stupor. The nursing orderlies became less afraid of them and more accepting. They were then transferred with their orderlies to a room on the admission ward. A period of laissez-faire then followed in which the whims and caprices of these tranquillized patients were indulged as far as possible and they were quite literally fussed over and petted. They were taken for walks, encouraged to play cards and games and to participate in occupational therapy. Within 2 months they were all transferred to other wards where they remained docile and pleasant.

The nursing staff, as in most periods of laissez-faire in psychiatric therapy, were much more disturbed than the patients and were fearful of their reverting to their former behavior. However, when they remained quiet and pleasant in their new surroundings, the tension of the nursing staff gradually relaxed and they learned to accept the change. One of the sections thus liberated has become an honor ward for a modified therapeutic community who receive just sufficient chlorpromazine to take the edge off their psychotic drives. Seclusion has thus been reduced to less than one-tenth and for days on end the remaining side-room section remains empty.

So much for chlorpromazine and reserpine. The promise of these 2 drugs had gradually converted me from a dubious dilletante to an avid enthusiast in the ataraxic field. It was with real enthusiasm that I commenced research on 2 new ataraxics: Frenquel and Pacatal.

Frenquel, which was given to 50 acute and 80 chronic psychotics, is the gamma isomer of Meratran, a central nervous stimulant without autonomic side-effects. In the course of toxicity studies it was discovered that this new compound made laboratory animals quiet and tractable. In 1954, Fabing(4) noted that it would prevent the development of experimental psychoses if given before LSD-25 or mescaline and would relieve the subjective symptoms of psychosis produced by these phantasmagorics. These dramatic results stimulated interest in the application of this new drug to the treatment of schizophrenia and in May 1955 Rinaldi *et al.*(5) presented a most encouraging report of the efficacy of Frenquel in the treatment of 39 disturbed patients with psychoses of long duration.

The following month I was able to obtain supplies of the new drug and proceeded to investigate it potentialities. At first we gave half our acute admissions, irrespective of diagnosis, Frenquel tablets alone with supportive psychotherapy. When injectionable material became available this was used at hourly intervals in quite high dosages.

In addition, 30 patients on a 59-bed ward of chronic disturbed patients, mostly severe schizophrenics who had failed to respond to any physical methods of treatment, were given 40 mg. t.i.d. To secure their cooperation in taking the tablets, I told the entire ward that we had a new drug that might help them to get out of hospital and that we were going to give it to the patients whose names began with the letters A to K and asked the L's to Z's to watch for the difference. This directive group therapeutic session was quite an experience.

Within 2 weeks of commencing treatment a striking change had taken place. The patients on Frenquel had become more sociable, they were neater, cleaner, and tidier. They looked better. Some chronic eczematous rashes cleared up. All their skins looked healthier and their eyes clearer. They gained weight. They stopped responding to their hallucinations. This was so encouraging that all the patients on the ward were given 40 mg. t.i.d. and within one week the ward became quiet and orderly. For the first time the patients would read books and magazines instead of tearing them apart. Curtains could be left up instead of being pulled down. Pictures were no longer destroyed and flowers could be left untouched in their vases. Yet there was no oversedation seen in the patients. They played cards together and appeared much more sociable and interested in their environment. Some who had previously banged their heads against the walls and covered their heads with their coats stopped responding to their hallucinations. It was most impressive.

It had been my plan to put half of these patients on placebos, but, as the delivery of these was delayed and we were running short of tablets, all the medication had to be

stopped. Within 4 weeks the ward gradually regressed to its former state. Fights again became frequent, complexions muddy and eyes lack-lustre. Hallucinations returned; no improvements were maintained. When the placebos, identically flavored and disguised arrived, they were given to the first 30 patients by the nursing staff who did not know of the substitution. The patients responded almost exactly as in their previous reaction to the genuine tablets. Had they been conditioned? Was this merely suggestion? It was all quite intriguing.

Meanwhile, the other patients, forlorn and dejected, rather pathetically held out their hands for the tablets and crept away dejected when refused them. So, we gave them the genuine tablets and they improved even more dramatically than the other 30 on placebos, some of whom had retained their hallucinations.

At present we are running a "double blind" study on 10 patients who appeared to benefit from Frenquel but who failed to maintain their improvement on placebos. Apparently 4 patients benefited.

To return to the admission cases. At first we appeared to be obtaining some very significant results but they were transient. Apparently the tablets, even in large dosages, were not effective. The intravenous injection of 20 mg. repeated half-hourly, produced a few slight improvements but they were not maintained. The 100 mg. injection, repeated hourly, helped a few patients to reorientate. One elderly schizophrenic complained bitterly that following the injection he felt lonely as his voices stopped talking to him, however, his loneliness lasted only half an hour. A few patients with senile confusional states became lucid for a few minutes after the injection. It was also possible to discuss delusional material fairly objectively with a few patients after injecting 100 mg. without their becoming as disturbed as they would have done previously. These positive results were obtained only by those physicians who still retained some enthusiasm over the new drug. Some sceptical colleagues obtained no results at all. What positive results we obtained could be duplicated by sodium amytal, chlorpromazine, or reserpine and we were having such encouraging results with Pacatal that our investigation was discontinued. However, we shall always be grateful to Frenquel for its complete lack of toxicity and the very forceful demonstration it gave us that we can never discount interpersonal relationships, emotions, and enthusiasms in psychiatric treatment.

The success of Phenergan, Diparcol, and chlorpromazine in pharmacology has focussed much attention on the phenothiazines and in 1954, a synthetic derivitive, N-methylpiperidyl-(3)-methylphenothiazine, was first tested and discovered to resemble closely chlorpromazine in its pharmaceutical action but to be much less toxic. Horatz(6) has reported on over 5,000 cases of the use of Pacatal, as the drug is now called, as a premedication in surgery. Kleinsorge(7) has used it with barbiturates in "therapeutic sleep," a modification of continual narcosis being extensively developed in Europe. We were fortunate in being the first hospital in Canada to be given supplies of Pacatal for clinical assessment of its place in psychiatry, and our studies started in June 1955.

After an initial personal test to make sure that the new drug could safely be administered, half the patients on chlorpromazine had Pacatal substituted in the same dosage and it was also given to one-third of the new admissions. Toxicity studies had shown a wide margin of safety, but for the first 3 months all the patients on the new drug had a weekly battery of liver, urinary, and blood tests and their temperatures, pulse and respiratory rates, and blood pressures were recorded thrice daily and they were weighed weekly.

In our experience with 250 cases to date we have found no evidence of liver or kidney damage; the pulse rate, blood pressure and temperature remain constant on normal dosage and though the white cell count fluctuates we have had no cases of agranulocytosis. Two patients have developed leukopenia; in one we discontinued the drug as at the time we had little experience of it; in the other we persisted with Pacatal as it was helping the patient and the white cell count gradually returned to normal. We now restrict our laboratory studies to a weekly white cell count and differential for the first

month and monthly thereafter unless the white cell count is abnormal. A careful physical check is kept on the patients and this is much more valuable than any laboratory studies.

There is always the danger that a noisy and aggressive patient who has forcibly been drawing attention to himself may become quiet and uncomplaining when put on the drug and so may be overlooked and may develop serious complications. This happened to 2 of our patients. The first, a veteran of 83, made a remarkable recovery from a recurrent manic episode in 5 days then we discovered that he had an atonic bladder and he required an in-dwelling catheter for one week. The second was a deteriorated young schizophrenic who developed severe constipation and a paralytic ileus that lasted 4 days. The complications that occur with Pacatal are associated with the drug's parasympatholytic effects. Nearly all the patients developed dry mouths and half of them had difficulty in accommodation. Their pupils became dilated and they had trouble in reading small print. This was generally associated with high dosages but did occur in a few patients on only 150 mg. daily. It affected younger patients more than the elder. We subsequently learned that if chlorpromazine were substituted for half the dosage of Pacatal, the symptom frequently cleared up. Constipation occurred in 10% and if this was overlooked the patients became quite toxic and starting vomiting. We now prevent the development of eliminatory complications by the routine use of laxatives and have prostigmine available for obstinate constipation and oliguria.

There were no cases of jaundice or extrapyramidal syndrome. In fact we found that Pacatal, substituted for half the dosage of chlorpromazine, cleared up the symptoms of Parkinsonism which frequently occur with chlorpromazine. This was presumably attributable to the atropine-like effect of Pacatal. No allergic reactions such as edema or rashes occurred though several patients had previously experienced such reactions on chlorpromazine. We found that the large dosages we used at first produced tremors, orthostatic hypotension, and mild pyrexia in elderly patients, who became quite confused and toxic. We now find that between 75 and 150 mg. daily will make these disgruntled and irascible old hypertensives much more pleasant and cooperative. One paranoid, resentful veteran of the Boer War, who had long been an administrative thorn in the flesh of our hospital, became pleasant and friendly within one week of treatment and has been maintained in a reasonable frame of mind on 100 mg. Pacatal daily for the past 9 months, despite an alcoholic cirrhosis.

We were unable to confirm Kline's(8) unfavorable report on the toxicity of Pacatal and we can only presume that he was investigating impure material.[4]

The method of administration was to give those patients who would cooperate 10 mg. tablets thrice daily. The dosage was then adjusted up or down till the desired degree of tranquillization was obtained. We found this varied between 75 and 900 mg. daily at first, when we were using rather high dosages. We now find that 600 mg. daily is sufficient to render the most excited patients quiet in 2 or 3 days. Intramuscular injections of the acetate are supplied in 2 cc. ampules containing 50 mg. This is diluted to 5 cc. with sterile water as saline precipitates it and is much less painful than an injection of chlorpromazine. I have given it intravenously in the pure form with no adverse results. We have given between 50 and 200 mg. daily by injection. It does not flatten the patient the way chlorpromazine does and he remains ambulatory but tranquil. We found Pacatal the treatment of choice in manic excitement and schizo-affective psychoses. Like all the other ataraxics, it is not indicated in depressions of the intensity encountered in psychiatric hospitals though it will help to calm the agitation of the involutional depressive and is an excellent adjuvant to ECT, shortening its course and preventing the development of postconvulsive confusion or aiding its resolution if it does arise. In the more chronic patients Pacatal was most effective in the symptomatic treatment of aggression, destructiveness, restlessness and insomnia.

[4] This has since been confirmed in a personal communciation.

In comparison with chlorpromazine it was found by both patients and volunteers alike to be almost twice as strong a tranquillizer and to have a slightly euphoriant effect. One patient said it was "like champagne after beer." The volunteers stated that it did not make them feel as heavy and drowsy as chlorpromazine but that it cut down their drive more and reduced their tension and hostility to the point that they were unable to enter into arguments. It was found to produce a vague feeling of restlessness and uneasiness when given to chronic severe anxiety neurotics whose reactions were characterized by palpitations and tremors, in other words, sympathetic overactivity. Apparently the parasympatholytic effect of Pacatal had still further increased their autonomic imbalance. We subsequently learned through experience that patients of pyknic build, who generally tend to show a parasympathetic response to anxiety by sweating and gastro-intestinal upset, benefited more from Pacatal than the asthenics, who respond better to chlorpromazine.

This was well demonstrated by 6 recurrent manics, all of whom had previously been treated in our hospital for manic episodes with chlorpromazine. They were all of pyknic build and responded more rapidly to treatment with Pacatal. Two recurrent manics of asthenic build were given Pacatal during the manic phase and though they improved gradually, their remission was much more rapid on changing to chlorpromazine. These results were confirmed by our experiences with acute schizophrenic psychoses, which characteristically occur in asthenics; these responded more rapidly to chlorpromazine than to Pacatal.

We are now obtaining excellent results in the treatment of severely disturbed psychotics by using Pacatal and chlorpromazine in equal dosage. Not only do the 2 drugs appear to act synergistically but they appear to be mutually anatagonistic to each other's complications. Perhaps the Funkenstein test might be a further help in deciding which drug to use or in what proportions. Certainly the alliterative aid "Pyknic-Pacatal," "Asthenic-Thorazine" (or "Lean-Largactil") has become a helpful guide in our application of this most promising new ataraxic.

It is my impression that the ataractic drugs work centrally by depressing the autonomic outflow and thus reducing the physical concomitants of anxiety. The patient, now freed from his sweating, tremors, palpitation, and gastro-intestinal upset, is able to take a more objective view of his emotional problems with which he may now cope with the aid of psychotherapy. In addition his drive is so much reduced that the fear of losing self-control is markedly diminished. Chlorpromazine, as a predominantly sympatholytic drug, is indicated in the asthenic who is prone to feel anxiety at an adrenergic level. Pacatal, a more vagolytic drug, is helpful to the pyknic, whose anxiety is frequently cholinergic in character. A combination of both drugs would seem to be indicated in those patients who lie somewhere in between these extremes.

After this review of the accomplishments of the ataraxics, it is time to take an objective view of their place in the psychiatric hospital. In their favor, let us say that for the first time our discharges outweigh our admissions, that the hospital atmosphere is calmer and more optimistic, seclusion is down to below one-tenth of its previous rate and ECT to one-third.

However, not one single deteriorated schizophrenic has been discharged as a result of these drugs. They just will not touch the hard bedrock case. This near-miracle, in our experience, can be accomplished only by lobotomy when the indications for this last-resort treatment are overwhelming. Now, before we submit any of our patients to lobotomy, we first try them on intensive courses of these drugs and a few patients show just sufficient temporary improvement to make us hold up their operations for a further period of reassessment and observation. This has significantly reduced the number of lobotomy operations in the last 2 years.

The general acceptance of these "wonder drugs" by the lay press and our own specialists has considerably stimulated the enthusiasm of our medical and nursing staff. In the course of research work on the back wards, we have come to take an unusual interest in the legacy of chronic schizophrenics bequeathed us by former therapists. An infectious air of optimism has been created in

the increased interest that research causes the staff to show in them. Even such mundane procedures as the estimation of blood pressures, pulses and temperature rates achieve an added significance when they are taken by an enthusiastic nursing sister, who, unconsciously, is anxious to give the research physician just what she thinks he ought to want and is equally as eager to obtain it from the patient by cajolery or flattery. It makes their work more interesting and adds a sense of achievement to what has often become a dull and monotonous task.

We, ourselves, objective though we think we are, by our very interest bring a feeling of sympathy and understanding to those chronic patients who have been doubly condemned for their failures firstly, to adjust to society and secondly, and much more heinous still, to respond to the treatment we had to offer.

These factors of interest, expectancy, optimism and enthusiasm must not be underrated in our appraisal of these new drugs. If they have done nothing else, the ataraxics have spurred us on to new efforts. In this age of anxiety, when the social acceptance of the material accomplishments of the individual far outweighs his psychic needs, we are likely to become dependent upon ataraxics more and more. The "emotional aspirin" is likely to become just as much a part of our way of life as the epileptic's anticonvulsant, the alcoholic's amphetamine, the executive's antacid, the salesman's hip-flask, and the socialite's sedative.

Summary

The ataractic drugs are so called from their ability to produce ataraxy: freedom from confusion and anxiety. In a veterans psychiatric unit of 550 beds with a high rate of admissions and discharges, chlorpromazine and reserpine have been intensively studied during the past 2 years and since June 1955, Frenquel has been given to 130 patients, and Pacatal to over 250, in an effort to clarify the indications for these ataraxics in the treatment of acute and chronic psychoses.

Our experiences with Frenquel are described in some detail as the originally hopeful and eventually disillusioning results obtained may explain many ambiguous findings in this complex field of research. Frenquel appears to have antihallucinatory and physically tonic effects in a small minority of regressed schizophrenics but to be of no value in the treatment of acute psychoses. Reserpine has also failed to fulfill earlier expectations. It is now reserved for the tranquillization of arteriosclerotics and as an adjuvant in the psychotherapy of some withdrawn schizophrenics.

Pacatal, a phenothiazine derivitive recently developed in Europe, and chlorpromazine are virtually interchangeable and synergistic. Pacatal is almost twice as strong a tranquillizer but a weaker hypnotic. It is mildly euphoriant and strongly parasympatholytic unlike chlorpromazine, a sympatholytic and depressant. Both are indicated in the symptomatic relief of psychomotor excitation, aggression, destructiveness, restlessness, and tension in acute and chronic psychoses. A combination of both, in which their mutually antagonistic autonomic effects reduce the incidence of complications and abolish the Parkinsonian syndrome, is yielding promising results.

In this study these drugs have significantly reduced the need for ECT and lobotomy without replacing these valuable methods of treatment. The seclusion of disturbed patients has been reduced to one-tenth. Since July 1955, insulin coma therapy has been replaced by group psychotherapy using ataraxics as adjuvants. Over twice the number of patients can be treated, so far with better results. Our discharges during 1955 outnumbered our admissions; the hospital atmosphere is calmer, and there is increased confidence and optimism. These latter factors cannot be ignored.

Alone, ataraxics merely modify symptoms but in conjunction with psychotherapy they open up wide vistas of therapeutic promise.

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DISCUSSION

GORDON O. PATTON, M. D. (Ste. Anne de Bellevue, Quebec).—In discussing the position of ataraxic drugs in the psychiatric hospital, Dr. Bowes has already stressed the importance of interpersonal relationships, emotions, and enthusiasms. I would like to suggest a slightly different emphasis on these factors by reference to the "hard core of disturbed and aggressive patients" and "the substitution of the ataraxics for insulin coma therapy."

Last summer 10 cases were selected solely on the criterion that they had the longest continuous terms in our side-room section, varying from 2½-77 months. Ataraxics were administered for 4 days. The patients were then moved to a large dormitory on our admission ward. Two nursing orderlies were with them. When the move was completed, a nurse aptly described the situation in these words: "It is peculiar to see all the patients so relaxed, while the orderlies look as if they are sitting on the edge of a volcano waiting for it to erupt." Fortunately no major eruption occurred and the tension subsided. The nurses responded to the challenge and rendered invaluable aid in assisting the orderlies to develop a variety of methods to control aberrant behavior. On a few occasions orderlies were transferred off the project in order to avoid the use of locked doors or any other kind of physical force.

Six weeks later these 10 patients were distributed to various wards throughout the hospital. Subsequent reassessment of each patient's behavior indicated definite improvement in 5, slight or no improvement in the other 5. It seems that these last 5 were maintained out of seclusion more as a result of change in staff attitude than because of a change in the patients. Change in staff attitude had been made possible by feeding ataraxics to the patients.

Support for this view is the fact that two weeks later, the 5 remaining secluded patients were transferred out of the side-room section with no special program or preliminary medication. Tolerance for aberrant behavior had increased as the staff had learned new methods of control. They had witnessed the demonstration that such things could be done. They now had the responsibility of maintaining their own prestige and self-esteem. The ataraxic drugs still play an important part, but this change in staff attitude seems equally important in keeping our side-rooms almost empty.

Last summer I was quite enthusiastic about the change from insulin coma therapy to the ataraxic push group. It certainly made work more pleasant and less rigorous in many ways. Great feelings of security are afforded both patient and staff when the most disturbed admission cases can be controlled on chlorpromazine within a few hours. At an early stage the patient can be given to understand that the controls will be returned to him as soon as he has the ability to use them. This is an excellent start in personal relationship therapy. But at present I find a definite lack of evidence that the duration of treatment or quality of recovery has been essentially different for our patients in these 2 groups.

I have the impression that during treatment the following differences have existed:

1. Some patients seem to reach a degree of improvement short of readiness for discharge, but then stagnate for weeks in a quiet, contented, seclusive state. In the ataraxic-push group I have yet to find a method to break up this stagnation. With insulin coma therapy the patient could usually be stimulated to further improvement by discussion or interpretation of his actions or his semistuporous remarks, at the time of awakening from comas. Analytically orientated interpretations flowed freely on such occasions.

It may be that insulin coma therapy is the treatment of choice for the quiet withdrawn patient, lacking gross physical evidence of tension.

2. There has been a change in themes of conversation during group therapy. In the insulin group the patients frequently ventilated their feelings of loss of self-confidence, inadequacies, past history, and various personal conflicts, with frequent reference to their experiences associated with the comas. In the ataraxic group a patient may use one session for such ventilation, but in general there is more emphasis on the theme that he was sick, is now better, almost ready to leave hospital and go to work.

This change of emphasis seems to suggest a somewhat different process of recovery, namely: (1) On insulin coma therapy, conflict material brought vividly into consciousness each morning may result in desensitization, so there is less need for psychotic defenses, and recovery ensues. (2) In the ataraxic group the emphasis may be on repression and reintegration. This very process of recovery may explain my difficulty in disturbing a plateau during therapy. The situation is very different when the patient's defenses are weakened each morning by comas.

In summary, I see some of the important functions of these drugs as: (1) An improved method of control of disturbed patients. This may create new feelings of security for both patient and staff,

thereby making possible or even initiating a different type of therapeutic community. (2) They make the patient more accessible to a therapeutic milieu.

BENJAMIN POLLACK, M. D. (Rochester, N. Y.).—The concentration on steroid chemistry, the investigation of the pituitary-adrenal axis, the indole and tryptophane derivatives, and the investigation of the metabolism of phosphorus show both consistent and varying results. The relationship of these substances to mescaline, lysergic acid, and other substances indicates that many of these products can produce grossly similar biochemical changes in the body and, according to their concentration, varying reactions in the human organism. This has opened wide speculation and hope that through biochemical and physiological means, the key to the mystery of the causation of mental illness may be solved. It must, however, be emphasized that mental illnesses, particularly schizophrenia, seem to be due to many causes and they show varying changes in the body, particularly in the responses of the adrenals, hypothalamus, and metabolites, not only among different schizophrenics but also in the same schizophrenic from day to day. Although many of the hallucinogens and psychomimetic drugs can produce some of the symptoms of schizophrenia, namely, hallucinations and depersonalization, it must be emphasized that these are only a small picture of the altered behavior and do not necessarily have the same fundamental implication of similar etiology. The studies of the effect of such drugs on serotonin have indicated some exciting possibilities, but its specificity and possible relationship to mental phenomena remain to be further investigated. Biochemical interaction and changes are findings in various forms of mental illness, but unfortunately are not consistent even in the same illness or in the same individual.

It is quite obvious that mental illness is the product of multifactorial changes which seem to be related to an interference with the major enzyme systems. It is quite evident that concentration on a unitarian approach will end in failure. It has been readily demonstrated that reversal of the chronic schizophrenic psychosis cannot be produced by the substitution or, indeed, the inhibition of a single factor found in research. The attempt to restore such autonomic control of the body by the use of parasympathomimetic or sympathomimetic drugs has ended consistently in failure.

Our experience at the Rochester State Hospital comprises 2 years' observation with over 1,500 patients given chlorpromazine, several hundred with reserpine, and smaller numbers given other drugs such as Meratran, Frenquel and promazine. It is interesting to note that the 2 original drugs, chlorpromazine and reserpine, still seem to have the greatest appeal and acceptance. The great variety of other drugs which have been produced in an attempt to mimic the action of these drugs have failed to produce higher therapeutic benefits. It is still our finding that chlorpromazine appears to produce the greatest benefits followed closely by reserpine. Frenquel (400 mgm.), Meratran, and similar drugs seem to be without value in the treatment of psychotics and we have abandoned their use entirely.

The foregoing papers report a wide variety of results from the use of other drugs such as Pacatal and promazine. It is important to remember that patients improved before electroshock and drug therapy were available. In estimating the results of treatment one must be aware of the statistical expectancy of spontaneous improvements without the use of such treatments. Thus the results here reported seem to indicate extreme therapeutic variations from the use of these products, from almost universal success to that of minimal or no results. It must be pointed out that the use of such drugs has been associated with an increased use of other factors which may play a fundamental role in the enhancement of the effects of such products. We have been impressed with the increase of good results when drug therapy has been considered as only one of a multitude of treatments in which psychotherapy and a total push program play a major role.

The use of terms such as antihallucinatory is to be deplored. It would, indeed, be näive to think of treating a single symptom of mental illness as if this were a unitary and unrelated finding. The exploitation of drugs based upon such expectancy has led to failures which should have been obvious.

One is impressed with the great variation in the therapeutic evaluation of these drugs. Since this field seems to hold hope, it would appear appropriate for this organization to appoint a committee to delineate certain clinical symptoms and changes in the body which can be evaluated and compared by various investigators. The need for the inclusion of similar factors appears obvious and would increase the comparative validity of reported results. The papers here presented indicate a feeling of encouragement and hope that perhaps organic and clinical research may hold the key to the future control of mental illness. It must always be remembered, however, that many of the reported findings are not the cause but the result of mental illness and that a single biological or chemical change is not primary but secondary. The resurgence of such investigation and the great emphasis upon the medical treatment of the psychotics is, indeed, an encouraging hope for the future.

REPLY TO FOREGOING DISCUSSIONS

H. ANGUS BOWES, M. D. (Ste. Anne de Bellevue, Quebec).—In answer to the many remarks that have been made concerning the toxic effects of Pacatal I am deeply sympathetic with the discussants. I went through the same phase last summer and at one time became so discouraged as nearly to give up my research with this powerful new drug, but we weren't killing anybody and we were doing some patients a lot of good, so I decided to deal with complications as they arose and was fairly successful in that we had only one major complication, which never recurred.

They say that beauty is in the eye of the be-

holder; perhaps the observation of symptoms carries with it this projective implication. In the investigation of new drugs one goes through phases of enthusiasm and frustration. We are looking for the universal panacea—the magic bullet. Here we have a new drug—it may be the answer to our problems—our enthusiasm mounts despite our superficial attempts at objectivity. Our results are proportionately better and then along comes a damning pronouncement by an authority as eminent in the ataractic field as Dr. Kline. It deals a severe blow to our confidence. We start looking for trouble and we find it. Mentally sick people are very much like children in their ability to sense indecision, fear and anxiety in their parent surrogates, which is the position that therapists and nurses play.

Of course, there are some unpleasant side-effects such as dryness of the mouth and failure of accommodation. However, the patients themselves, in my experience, regard this as a trivial price to pay for the ataraxy they are experiencing. This symptom can be ameliorated by an old-fashioned combination of glycerine and lemon juice. At least it means that most of them will take in adequate fluids because of their intense thirst.

With regard to the eliminatory complications, some of our patients are so regressed that they are unable to give any account of their excretory processes. It is an unjustifiable intrusion to have our nurses and orderlies checking on their toilet activities all the time. However, we did give them laxatives as a routine and in cases of suspected severe constipation, however dynamically oriented you are, do not hesitate to slip on a rubber glove, insert a digit and see if there is any obstipation there. It is better to risk the exacerbation of a psychosis than to invite a paralytic ileus.

With regard to atonic bladder—these patients are thirsty, give them lots of fluids and if anything goes wrong don't hesitate to discontinue or reduce the medication and try prostigmine; you will get some results with that. Above all, realize that laboratory reports are inadequate and tardy substitutes for clinical observation, though it is much easier to read a green slip from the laboratory than to go up and look at a patient. I think we must have confidence in our clinical judgment to cope with emergencies as they arise and to prevent their recurring. Lack of clinical acumen will only lead to the misuse of what appears to be a most promising ataraxic.

A TWO-YEAR EVALUATION OF CHLORPROMAZINE IN CLINICAL RESEARCH AND PRACTICE[1]

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With each announcement of a new drug for the treatment of mental illness, there is an accompanying flurry of optimistic excitement and magical expectation. Encouraging progress reports and glowing predictions from some of the nation's leading newspapers and popular magazines contribute to the atmosphere of rising hope.

The passage of time carries with it a sobering objectivity. It allows the opportunity for repeated clinical trials and follow-up studies so essential for the proper evaluation of new compounds.

It is difficult to estimate the time necessary to assess adequately a new drug. With compounds that show little or no clinical activity the task is simple and they may be discarded after a brief pilot study of several months or less. But with medications that demonstrate genuine promise the problem becomes much more complex. Probably 2 to 5 years are required before an adequate appraisal of clinical effectiveness can be made. The elements of suggestion, which to some extent, can be eliminated earlier by double blind studies have by this time spontaneously been dissipated. Side-effects or complications, sometimes delayed in showing themselves, have by now made their appearance and can be weighed against the positive benefits of the drug.

Chlorpromazine stands as an example of that new group of tranquillizing agents which have shown considerable merit and now are in need of further careful scrutiny. Our own experience with chlorpromazine extends over a 2½-year period, barely enough, perhaps for a retrospective evaluation. We recognize, however, that our appraisal is but an interim revue and that the final word will not be written for some time to come.

We should like to stress from the outset that this is a clinical paper. We have studied over 300 cases receiving the drug from 6 weeks to 24 months. Some of the latter group continue to receive the drug at present. We began our investigations with the German product Megaphen before chlorpromazine was available in this country. Our early cases, since we were experimenting with a new drug and wanted to observe its psychic effects and toxic properties directly, were not controlled. We are not, therefore, presenting statistical data based on double blind studies. The material covered is the result of careful observations and follow-up. On this basis, we feel it has clinical significance.

Another point we should like to stress is the nature of our patient group. One-third of our patients were hospitalized and the remainder were outpatients. The vast majority of our inpatients were voluntary admissions, predominantly pseudoneurotic schizophrenics. This group showed a great deal of pan-anxiety and subjective tension, but motor manifestations such as hyperkinetic or assaultive behavior were minimal or absent. Even the small number of overtly schizophrenic patients in our wards differed from many such patients seen in state hospitals in that they were readily manageable, were not hyperactive and did not require restraints because of destructive behavior.

Our outpatient group contained a mixture of neurotic, pseudoneurotic, and ambulatory schizophrenic patients as well as a number of depressed patients. They were fairly typical of the type of patients seen in a big city psychiatric outpatient clinic and some metropolitan private practices. It is most important to keep this type of patient material in mind, since the difference between our experiences and others may be in part accounted for by the difference in patient material.

[1] Read at the 112th annual meeting of The American Psychiatric Association, Chicago, Ill., April 30-May 4, 1956.

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METHOD OF ADMINISTRATION

Initially we followed the hibernation technique of Delay and Deniker but found with our material we could not duplicate the hibernation state. Some of our patients even with doses up to 2,400 mgm. daily were able to walk about freely and showed minimal drowsiness or other side-effects. At first, we kept our patients on strict bed rest for a week during the period of intramuscular injection. We soon found that the oral medication was just as effective as the I.M. and reserved the latter only for uncooperative patients. We also discontinued the bed rest when we found the danger of hypotensive plenomena to be considerably less than we had expected. We were seldom troubled by it except when certain sensitive patients would suddenly change from a lying to a sitting or standing position.

We eventually developed the following regimen which we have continued to the present time:

Patients are started on a dose of 50 mgm. t.i.d. the first day and raised by 100 mgm. daily to 1,000 mgm. or more. The dosage is raised to the point where it eliminates symptoms and toxic side-effects appear. It is then gradually reduced by 50 mgm. daily to the lowest level that will keep symptoms from recurring. The patient is then maintained on this level for varying periods depending on his clinical needs. Our maintenance doses have varied between 75 and 2,400 mgm. daily. There was a marked individual variation in therapeutic responsiveness as indicated by this wide range in maintenance levels. The majority of patients who responded to this regimen did not require a maintenance dosage over 600 mgm. daily. Above this dosage the incidence of side-effects increased sharply. Sweeping statements to the effect that only very low or very high dosages are effective do not appear to be warranted.

TYPES OF RESPONSE

What is the nature of the improvement and which conditions respond best? It is by now well known that the great advantage of the tranquilizers is their ability to produce a calming effect with a minimum of drowsiness and absence of confusion. Comparable doses of barbiturates to produce the same degree of relaxation and diminution in motor activity frequently result in drowsiness to the point of sleep. It is not our intention here to speculate on the physiology or site of action of the drug in the brain.

It was our experience that the more overtly disturbed was the patient, the more effective was the action of chlorpromazine. Calming effects in patients in whom motor manifestations of anxiety were minimal or absent were far less consistent than in agitated or combative patients. This observation transcended diagnostic boundaries. Since most of our patients, both hospitalized and outpatients fell into the less disturbed group, results with chlorpromazine alone were frequently disappointing. This was especially true with the "garden variety neurotic" whose predominant symptoms were expressed in the form of phobic mechanisms, hypochondria, or obsessive preoccupation.

Anxiety was found to be reduced in some patients but not in others. Obsessive rumination was usually little affected. Depersonalization phenomena were frequently intensified. More will be said about this below. The response in phobic patients was extremely variable. In some, the phobic anxiety was considerably reduced, but in others the taking of the drug itself became involved in a phobic avoidance when unpleasant side-effects developed. In a number of instances paranoid ideation weakened while the patient was receiving the drug. In a few others it was intensified, apparently in relation to the side-effects. In ambulatory schizophrenic patients with little or no drive the results were uniformly poor, with virtually no effect on the quality or intensity of the symptoms.

Our experience with depressions has been frequently disappointing and always unpredictable. Only a very small percentage of patients who were depressed improved on chlorpromazine alone and some became much worse. Chlorpromazine combined with the amphetamines gave better results but even with this addition, fewer than 50% of these patients improved. Agitated depressions responded better than the quiet withdrawn group. In some instances the agitated features would be diminished with the drugs

but the underlying depression remained. Electroshock still appears to be the treatment of choice for depressions. We have found no evidence in our material that giving chlorpromazine with electroshock appreciably shortens the course of ECT.

CLINICAL COURSE

In some patients who showed improvement with the drug, relapses occurred both while receiving medication or shortly after its discontinuance. In patients who relapsed while receiving the drug, raising the dosage sometimes resulted in a return of the improvement. In others an adaptation seemed to take place and no further improvement was forthcoming. Some of these patients, when started on other phenothiazine derivatives without their knowledge once again improved. It is still impossible to predict, with any degree of statistical validity, how many patients can have the drug discontinued and how many will have to be kept on it indefinitely. We cannot confirm the observations of others that the majority of patients do not need some form of maintenance dosage, even when receiving accompanying psychotherapy.

The early literature admonished against combining barbituates with chlorpromazine, speaking about 3- to 5-fold potentiation. We have found that with patients receiving 400 mgm. of Thorazine daily or less, we can prescribe pentobarbital in 0.1 gm. capsules without incident. This has frequently been necessary in that group of patients receiving Thorazine who did not become drowsy or derive any sleep-producing benefits from the drug. Intravenous barbituates and Thorazine would appear to us to be still too dangerous to combine without extreme caution.

We have combined chlorpromazine with Serpasil and found no advantage to this combination. Again we wish to stress that this may be in relation to our case material with its large representation of pseudoneurotic schizophrenics. In our experience, chlorpromazine had a more rapid action than Serpasil with psychic side-effects such as depersonalization and depression being less frequent. In spite of the fact that the physiologic side-effects of oral chlorpromazine are greater than those of oral Serpasil, they were not serious and we found it to be more effective clinically than Serpasil by mouth. Intramuscular Serpasil, however, has compared favorably with I.M. chlorpromazine.

SIDE-EFFECTS

In the same way that there is a marked individual variation in the therapeutic effects and dosage, there is also a marked variation in the incidence and intensity of side-effects. As a general rule, however, more complications develop on higher dosages than lower ones.

The most common side-reactions encountered were drowsiness and fatigue. Some patients became very drowsy and weak on only 150 mgm. daily while others showed little evidence of drowsiness on a daily maintenance dosage of 1,000 mgm.

The Parkinsonian syndrome has occasionally developed on dosages as low as 150 mgm. daily but we rarely have seen it on maintenance doses of less than 500 mgm. daily. On the other hand, several patients receiving over 1,000 mgm. daily for a month showed little or no evidence of Parkinsonism. In our own material, all patients with a marked Parkinsonian picture have returned to normal within a week after discontinuing the drug, although we have learned of instances from our colleagues where the symptoms persisted for over a month after the drug was stopped.

Jaundice was an infrequent complication in our series. Its occurrence seemed to bear no relationship to the amount of medication, occurring on both high and low dosages. There was no consistent temporal pattern since it developed both early and late in treatment. Several patients who had developed jaundice on earlier courses of chlorpromazine therapy did not have a recurrence of the condition on a second course of the drug later on.

We have observed one case of agranulocytosis unquestionably associated with chlorpromazine administration. The condition developed in a middle-aged male after only a week of the medication. The patient received a maximum of 400 mgm. daily. Most cases of agranulocytosis, regardless of the etiologic

agent, begin to develop during the first week of drug therapy. Therefore it is wise to observe the patient carefully for fever, sore throat, or dysphagia during this period, and to obtain an immediate blood count if these symptoms develop.

Since fewer than a dozen cases of agranulocytosis have been reported in over 4,000,000 patients receiving the drug, the safety factor remains quite high. These figures lead one to speculate that the agranulocytosis observed was due to a nonspecific and as yet unknown sensitivity of certain individual patients rather than any specific leukocyte destroying property of the drug. We continue to take monthly routine counts on our patients, chiefly for medico-legal purposes.

In addition to these side-effects, we have observed a syndrome not before reported to our knowledge. This was a reaction seen only in a half-dozen patients early in our observations in the spring of 1954. It was a myasthenia gravis-like reaction in which the patient developed a choking sensation in his throat, difficulty in swallowing and chewing, a thickness of the tongue and slurring speech, with occasional respiratory embarrassment. We were considerably alarmed by this and administered prostigmine with equivocal results. Fortunately the condition was self-limiting and we have never seen it again. It may have been related to the particular batch of chlorpromazine we were using at the time.

An interesting observation in our outpatient group was that many patients refused to continue the drug and discontinued its usage of their own accord usually within the first 2 or 3 days. This could not happen in our hospitalized group because of hospital discipline. Those outpatients who discontinued the drug usually did so because of an increase in their anxiety associated with marked weakness, drowsiness, aches and pains, or feelings of depersonalization and depression. We have seen the development of depression where it had not existed before and the deepening of a depression already present. In addition, both inpatients and outpatients developed acute psychotic reactions with the drug characterized by intensification of unreality feelings already present and the development of hallucinations and delusions. These subsided in 2 or 3 days after the drug was discontinued. Precipitation of psychosis was perhaps more of a problem in our patient material than in some other types of case material. Because of this ever-present danger, however, it is most important to screen patients carefully and observe them closely in the early days of the drug administration.

CHLORPROMAZINE AND PSYCHOSURGERY

Claims have been made that chlorpromazine acts as a chemical lobotomy and dispenses with the need for psychosurgery. We wish this were true but unfortunately have not found it to be the case. While a number of previously hyperactive patients can be kept tranquilized almost indefinitely with the drug, there is a large group of patients, especially among the pseudoneurotic schizophrenia group, with unbearable anxiety and motor tension in which the hyperactivity factor is minimal. These patients do poorly with all forms of treatment, including chlorpromazine, but a large percentage have shown a quantitative diminution in the level of their anxiety with resultant improved function after psychosurgery.

Chlorpromazine has been helpful in controlling the excitement stage occasionally seen in the first few days following lobotomy. It has aided in dispensing with the need for restraining sheets in such instances.

BLOCKING ACTION OF CHLORPROMAZINE IN MODEL PSYCHOSES

One of the most provocative research applications of chlorpromazine has been as a blocking agent against the hallucinogens. Over 50 patients have thus far been studied. Visual hallucinations and depersonalization phenomena associated with mescaline and lysergic acid administration have been reversed within a matter of seconds in a most dramatic fashion by the intravenous injection of 15 to 50 mgm. of chlorpromazine. We have also used intravenous azacyclonal (Frenquel) in 100 mgm. doses for the same purpose. Its action has not been as prompt, sustained, or as clear as chlorpromazine's. Precipitous drops in blood pressure with intravenous chlorpromazine have rarely occurred, although gradual B.P. drops of 20 to

30 mgm. systolic and diastolic occasionally have been noted. Drowsiness, associated with more rapid administration of I.V. chlorpromazine, was not observed with intravenous azacyclonal administration. The combination of sodium amytal and Desoxyn intravenously ranks between Frenquel and chlorpromazine as an antidotal agent. None of the blocking agents developed to date can be considered specific.

CHLORPROMAZINE AND PSYCHOTHERAPY

There is an increasing number of psychiatrists today who believe that the ideal therapeutic combination of the future will be psychotherapy and drugs. What role chlorpromazine has played in the facilitation of psychotherapy is still to be evaluated.

Rather than any direct effect upon such factors as insight, suggestibility, or affect, chlorpromazine appears to offer greater accessibility to the patient by quantitatively diminishing the level of anxiety present. This frees the patient from the intensity of his self-preoccupation and introspection and allows him to focus outward on the therapist and what he has to say. In some instances, chlorpromazine will afford a severely phobic patient who previously was unable to travel to the psychiatrist, the opportunity to get to his doctor's for therapy thus obviating the necessity for hospitalization. In such instances the drug is of unquestioned value. But there are other instances in which chlorpromazine appears to impede psychotherapy rather than benefit it. For example, hypochondriacal patients may react very strongly to such side-effects as weakness, muscle aches, drowsiness, and feelings of depersonalization. They may center their attention on these symptoms thereby deflecting their attention from those psychodynamic factors of more vital significance in their illness, and begin to generate more anxiety and tension. Instead of the drug serving to benefit the patient in such situations, it has actually become an obstacle to progress and an iatrogenic source of concern.

Where overt anxiety does not appear to be present as a major symptom we have not had the impression that chlorpromazine has shortened the duration of treatment or made the patient any more accessible or responsive.

Many variables enter in to distort such an evaluation. The elements of suggestion and spontaneous remission must be taken into account. We prefer to use the patient as his own control since this tends to eliminate subtle differences in handling from patient to patient and gives us a uniform baseline to check against.

We are continuing the search for tranquillizing agents with a broader scope of effectiveness and a minimum of side-effects. One of these, piperidinochlorphenothiazine, was extremely effective as a tranquilizer until we discovered one patient who developed eye findings resembling retinitis pigmentosa. This forced us to discontinue its usage. Since then there has been a number of other reports of this same condition from different parts of the country. Fortunately, we have never seen a case of this nature associated with chlorpromazine.

The same compound, with the addition of a brom radical, brompiperidinochlorphenothiazine, has shown promise as a tranquilizing agent and to date has not given rise to any eye complications.

SUMMARY

In conclusion, we believe that chlorpromazine has established itself as a useful therapeutic tool in the treatment of mental illness. It is a relatively safe drug, and although the side-effects are many, serious or permanent sequelae are almost unknown. In regard to its therapeutic effect in our case material much is left to be desired. Its range of application appears to be narrow, being most effective in agitated, hyperactive, and overtly anxious patients, with much more limited value in depression, or with obsessive patients manifesting little or no increase in motor function. It is palliative rather than curative. It can intensify anxiety and precipitate depression and psychotic symptoms as well as alleviate them. Its major advantage lies in its tranquilizing action without accompanying marked drowsiness or confusion. Its value as an adjunct to psychotherapy is still to be evaluated.

Chlorpromazine has been a major force in firmly launching us into the era of psychopharmacology. We are still suffering, however, from all the uncertainties and hesitation

of a pioneer venture. This should not deter us from continued investigation and progress.

DISCUSSION

WERNER TUTEUR, M. D., (Elgin, Ill.).—It is becoming more and more evident that psychotics react better than neurotics to the so-called newer drugs. For this there may be two reasons. Psychotics are usually confined to institutions where under a controlled regime the use of drugs is the rule. On the other hand, it seems to be especially the acuteness of a psychotic illness that makes for a better response than a neurosis which has become chronic and crippling. It has been the experience of several investigators that neurotics quickly apply their doubts to the efficacy of the drugs, a phenomenon which has not been observed in the acutely disturbed psychotic. This, of course, does not cover the psychotic patient disturbed to a degree that he will not cooperate in taking the drugs, making parenteral medication necessary.

The question still remains as to how long a patient should remain on these drugs, once social recovery and symptomatic improvement have been reached. A study presently undertaken at Elgin State Hospital on discharged patients who had reached social recovery, indicates that constant adjustment and readjustment remain necessary, even 9 months after discharge, to prevent relapse as well as side-effects. A special chlorpromazine-reserpine clinic serves this very purpose.

Regarding the treatment of morphine withdrawal, reports differ widely as to the efficacy of chlorpromazine and reserpine. Such investigations should be carried out only under conditions where the patient is completely isolated. Possible availability of contraband is always present if this prerequisite is not fulfilled. Reports by Frazer and Isbell (J. Pharmacol. & Exper. Therapeut., 116:21, Jan. 1956) of the National Institute of Mental Health, Addiction Research Center, Lexington, Kentucky, claim that both drugs are ineffective in this area.

The combination of Frenquel with reserpine sounds promising, although, as in any combination, individual adjustment of the combination factors to each other is essential.

Frenquel and other ataractic drugs may have a beneficial effect on "ectodermal diseases" other than the neurological and psychiatric entities. Spinka (Ill. Med. J., 109:128, Mar. 1956) has observed good results with chlorpromazine in psoriasis, and Ferguson has observed the same with Frenquel. Further reports on dermatological syndromes responding to ataractic drugs may be revealing.

Consistent reports of follow-up psychotherapy after and concomitant with ataractic drugs so far are missing.

Both Winkelman and Malitz mention that anxiety reactions respond best to chlorpromazine, a fact which has been amply borne out by most investigators. It would be interesting to know the symptomatology of the two cases of obsessive reactions in Dr. Winkelman's paper who responded to chlorpromazine, inasmuch as obsessive-compulsive illness remains the stepchild of all therapy. We have not been applying stimulants in combination with chlorpromazine, such as dextro-amphetanin, to combat drowsiness, but prefer to either decrease or discontinue chlorpromazine.

We are especially interested in the patients suffering from C.N.S. syphilis associated with hyperactive behavior, as Winkelman mentions them. Himwich, in a recent paper on the management of disturbed mentally defective patients, all of them suffering from organic brain disease, points out that such patients may be more sensitive to tranquilizing drugs than others and may respond to lower dosage. Regarding the withdrawal of chlorpromazine, we gradually diminished the dosage among the once combative and destructive chlorpromazine-treated patients in our special chlorpromazine-reserpine clinic, and just one week ago we replaced chlorpromazine with placebos on 2 patients who had been away from the institution 5 and 7 months, respectively, and who were making exemplary adjustments. Whether or not maintenance therapy must be continued indefinitely is presently subject to a special study at Elgin State Hospital. It is surprising that Dr. Winkelman has not observed a full-blown case of Parkinsonism in his chlorpromazine-treated patients.

We fully agree with Dr. Malitz that a minimal period of 5 years is necessary for an adequate appraisal of the tranquilizers.

Hoch (Chlorpromazine and Mental Health. New York: Lea & Febriger, 1955) already pointed out in his paper, "The Effect of Chlorpromazine on Moderate and Mild Mental Emotional Disturbance" given in Philadelphia, June 6, 1955 (Meeting: Chlorpromazine and Mental Health), that compulsive patients did not show much response to the drug and that only 20% of other types of neurotics lost all their symptoms. He was equally discouraging about the treatment of depressions with chlorpromazine, and found that chlorpromazine was more effective in controlling hyperactivity, tension, and anxiety. The combination of chlorpromazine with electroshock is frowned upon by Kalinowsky, who recently reported several fatalities with this mode of treatment. Regarding the combined use of chlorpromazine with reserpine, we have used it extensively in relationship of 100 mg. to 1 mg. We found that of 74 highly disturbed psychotics 10 treated, 30 patients, or 40.5%, developed side-effects, most of these being within the Parkinsonian syndrome. It is generally agreed that chlorpromazine acts faster than reserpine, as was stressed by Malitz, and our own study showed that the highly overactive and destructive patient needs an average of 38 days of chlorpromazine, but 54 days of reserpine to reach appreciable improvement of these symptoms. It likewise appears to be a fact that dosage and duration of administratoin are not related to the development of side-effects, as pointed out by Malitz and others. Regarding agranulocytosis, we had one fatality which occurred after 5 weeks of taking 100 mg. of thorazine twice a day.

Healthy conservatism, combined with the innate enthusiasm of the investigator, assisted by painstaking methodology and strictest self-criticism will, in the end, render an adequate evaluation of these drugs as the years pass by.

METHYL-PHENIDYLACETATE HYDROCHLORIDE (RITALIN)[1] IN THE TREATMENT OF CHRONIC SCHIZOPHRENIC PATIENTS

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In determining the effectiveness of a method of therapy, the nature of the group being treated must be considered. Since it has been stated that 80% of those who are to be discharged following hospitalization in a mental hospital will be discharged within the first year, any treatment method tried on recent admissions will be more successful than the same or any other method tested on patients hospitalized more than a year, if discharged from the hospital is the criterion for marked improvement. Kramer's(3) findings that the likelihood of discharge after 2 years was no greater in 1950 that it was in 1916 emphasizes even more the importance of considering the history of the group being tested.

Perhaps in no other field do subjective opinion, the investigator's enthusiasm, and the salutary effects of attention require the simultaneous use of placebo medication as in the determination of the effectiveness of a therapy for the mentally ill.

Therefore, in this clinical evaluation of methyl-phenidylacetate hydrochloride, hereafter referred to as Ritalin, the group of patients on whom the drug was tested must first be considered. They were a group of 50 chronic schizophrenic patients, hospitalized an average of 12.6 years, 25 male and 25 female, in whom no previous therapy had produced any lasting effects.

Alternate unselected patients were given Ritalin or an identical appearing placebo. The code was known only to the hospital pharmacists and a staff physician who evaluated any side-effects, this physician did not determine any change produced by the medication.

A control evaluation of all the patients, done by the same psychiatric nurse before the procedure was initiated, was recorded on a standardized form which included verbatim responses to determine orientation, insight, the presence and content of delusions, and energy output. Three different evaluation forms were tried before one which produced significant and descriptive results was evolved. No check list sufficiently complete to record significant behavior and remain within the limits of practicality was found; instead the psychiatric nurse made a note of the patient's behavior on entering the room and his attitude before and during routine questioning. These notes were evaluated weekly during the course of the trials by the same psychiatric nurse.

The intial dosage was 30 mg. a day given orally in 3 equal doses of either Ritalin or placebo. After one week the daily dose of Ritalin was increased to 45 mg., after 2 weeks to 60 mg., after 3 weeks to 90 mg., and during the final week to 120 mg. each day. The placebo and Ritalin were increased by equal amounts at the same time. All other medication was discontinued 2 weeks prior to the start of the test.

To avoid the likelihood of those being treated receiving added or different attention, they all remained on the same ward and followed the same routine during the trial period. It was of interest that the patients showed only a passive interest in the medication; but some of the ward personnel took, tasted, smelled, dissolved and broke the medication in an effort to determine which was the placebo and which the Ritalin.

RESULTS

Six patients showed behavioral change as measured by their becoming more active; however, this increased activity could be considered improvement in only one patient. This individual appeared less agitated, showed more appropriate behavior and mood,

[1] The Ritalin used in this evaluation was supplied by the Ciba Company.

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and initiated conversation spontaneously when interviewed which she had not previously done. The other 5 were more active by such measures as the amount of time they spent standing or pacing compared with their previous total inactivity; or showed less concern over their delusions but their thought content and speech did not become more appropriate. Another patient became more verbose but no less bizarre; and the change was considered an increased production of abnormal thought content rather than evidence of improvement.

A striking finding in this study was the degree of stereotypy in the thinking of these schizophrenic patients. Several gave varying inappropriate answers to standard questions, and the same inappropriate answer was given verbatim to the same question when it was repeated a week later.

In 4 of the 50 patients, their condition was clearly aggravated during the period of observation. Three of these 4 were taking placebo and showed an increase in their symptoms, became more agitated or were less cooperative. Similar exacerbations in their illness had been previously noted.

Twenty-two of the patients taking the placebo and 10 of those taking Ritalin showed no measurable change in behavior during the treatment period.

SIDE-EFFECTS

The only significant side-effects noted involved the gastro-intestinal system. Seven of the 25 patients who received Ritalin and 1 who received the placebo were reported by the ward personnel to have shown a decrease in appetite; one of these had to be fed whereas he had previously eaten spontaneously. All (7 on Ritalin and 1 on placebo) complained of abdominal discomfort. These symptoms appeared during the second week and were complained of intermittenly during the course of the trial. A complete blood count at the termination showed no depression of the formed elements of the blood. Four of those receiving Ritalin demonstrated the following weight loss following 5 weeks of treatment: 6 lbs., 11 lbs., 13 lbs., and 18 lbs.

CONCLUSION

In this group of 50 chronic schizophrenic patients, half of whom received Ritalin and half an identical appearing placebo the Ritalin was without demonstrable effect. Six of those on Ritalin showed a decrease in appetite, abdominal discomfort, and weight loss during the test.

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WAYS OF AMERICAN PSYCHIATRY

Report from Brazil

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Dr. José S. Rocha of Rio de Janeiro, who recently made a survey study of psychiatry in the United States, published his report in *Correio da Manha*. Following are his impressions:

Modern American psychiatry is very proud of its psychosomatic concepts and of the value it attributes to the cultural factors. But it emphasizes too much the psychological factors, not evaluating adequately the bodily factors in the genesis of mental illness. As Leo Alexander, one of the best-informed American psychiatrists, emphasized in his book, *Treatment of Mental Disorder*, in the American psychosomaticism the primacy belongs always to the psyche which performs the role of the "big brother," while the soma is nothing more than the "little ignorant brother." This book is being translated into Spanish.

As an example, I refer to the case, observed by Dr. Samuel A. Kirk, of the 12-year-old school boy, who presented bad behavior between periods of meals correlated with a low rate of sugar in his blood. Dr. Kirk obtained 3 psychiatric diagnoses, one saying there was a traumatic experience of early infancy, until a common-sense doctor suggested a blood sugar test.

Modern American psychiatry, as taught at the university and as practiced in the hospital, seems to be totally psychoanalytic. Emotional conflicts, defense mechanisms, guilt feelings, and anxiety are the principal factors in the composition of mental disorders. Neuroses and psychoses are determined by the same psychological factors. Schizophrenia, for example, is a kind of *reaction*, like depressive, obsessive-compulsive, etc., *reactions*.

Influenced by the anthropologists' works, American psychiatry evaluates the social and cultural factors. Thus, the emotional conflicts would be primarily determined by aggressivity and hostility and not by sexual impulses, as stated in the primary Freudian view. Neuroses, according to Karen Horney, are products of American cultural environment, ways to react within the socially accepted patterns to the great and conflictive exigencies of American life. Neuroses are thus dependent on the present life situation and interpersonal relations rather than on the preformed instincts as Freud thought. Harry Stack Sullivan, one of the most praised American psychiatrists, thought in the same way when he said neurotics (and even psychotics) are not sick people, but persons who have problems, and feel embarrassments in dealings with others and unconsciously or consciously defend themselves against these embarrassments, acquiring new problems.

There is no doubt that psychoanalysis and the various psychodynamic approaches derived from it open new perspectives for the interpretation of mental illness and better understanding of man. With psychoanalysis we become free of determinism, a kind of fatalism that existed in the past century. But, will there be only these ways, the psychodynamics for comprehension of mental illness, or will there be others, perhaps more fecund and not yet found by American researchers? These ways exist, but are covered by an avalanche of publications on psychoanalytic or psychodynamic subjects. Such matters overflow into plays made in Hollywood and novels that are best-sellers of the moment.

Beyond this modern demonology, as Norman Reader called it humorously (*Six Approaches in Psychotherapy*), in which the devils have other names—aggressivity, hostility, guilt feelings, anxiety—and must be exorcized, new ways are being opened by American researchers, connected with the psychobiology of William McDougall and Adolf Meyer and the vitalism of Abraham Myerson, in which the causes of mental disorders are multiple and mind and body are one. Researches in socio-environmental factors, educational processes in mental health, and the physiology of the nervous system are being carried on in many centers in the United States.

ADVANCES IN MANAGEMENT AND TREATMENT IN EUROPEAN MENTAL HOSPITALS[1]

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In a survey on English mental hospitals made in 1947, Pratt stated that English psychiatry is more "mental hospital centered" than is American psychiatry. This is still true, and applies to psychiatry in all European countries. There is, however, much evidence that American psychiatry takes an increasing interest in mental hospitals. On a national level the newly organized Joint Commission on Mental Illness and Health, headed by K. Appel and L. Bartemeier, and on a state level such plans as outlined for New York by P. Hoch in a recent paper on "Psychiatric Aims and Policies" examplify this trend. In the light of these developments it is of interest to investigate the status of mental hospitals in other countries, and to see which advances made in management and treatment might be of value for our own efforts in this field.

This presentation is based on numerous visits to psychiatric facilities abroad and on a more systematic study made in England and Switzerland last year. The reason for the emphasis on these countries is that English mental hospitals function under the same legal restrictions regarding the admission of patients as ours do, while Switzerland is a good example of a country without any commitment procedures. The actual functioning of mental hospitals in these two countries and their admission and discharge rates do not seem to be influenced by such legal differences. They have in common that they function in an atmosphere of confidence on the part of the general public and the press, and most deviations from our own mental hospitals can be explained by this public support.

The curiosity of the foreign visitor is immediately aroused by some surprising statistical figures. The population of England and Wales is approximately three times that of New York State. In New York with a population of 15,000,000 the number of hospitalized mental defectives is about 20,000. In England and Wales with 3 times the population of New York a proportionate number of about 3 times as many mental defectives are hospitalized. Contrary to this incurable group the inmate population of all other mental hospitals is approximately 100,000 in New York, but only 150,000 in England and Wales, which means that an area with 3 times the population of New York needs only one and a half times as many beds for mental patients. Figures for other countries are equally favorable. This difference cannot be explained by a lower incidence of mental illness because the turnover in European institutions is much higher than in this country, and a larger number of patients is returned to the community. The reasons for this favorable picture should be discussed.

One great difference is the absence of legal restrictions for admission to mental hospitals in the continental countries and the avoidance of existing restrictions in England. The English "Mental Treatment and Lunacy Act" provides for Court Certification similar to ours, but the vast majority of mental hospital patients are admitted as voluntary patients, and hospital directors take pride in a high ratio of voluntary admissions. In some hospitals their number is 80% to 90%. In 1953, the last year for which comparable figures are available, the English hospitals had an average of 69% voluntary patients, while New York listed only 6.8%. That this does not depend on the type of patients, but on medical and administrative practice, is illustrated by the fact that in England herself the percentage of certified patients showed wide variations from only 5% in some progressive hospitals to 40% in others. Certification is used as a last resort, and the figures for voluntary patients are even more significant when we realize that facilities for active outpatient

[1] Read in the Section on Mental Hospitals at the 112th annual meeting of The American Psychiatric Association, Chicago, Ill., April 30-May 4, 1956.

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treatment keep many patients outside the hospital who would enter voluntarily. Furthermore, some hospitals with 80% and 90% voluntary admissions have nonstatutory patients in newly established annexes which have the status of a general hospital; they are given a different name but are staffed by the mental hospital. While a voluntary patient still has to sign a legal form, this is not necessary in the annex, thus making it still easier for the patient and the family to accept hospital treatment. Another means to increase voluntary admissions is the newly introduced "Urgency Order," a certification for 7 days, used in psychoses which are expected to clear up within this time. It is being applied mainly for infectious, toxic, or posttraumatic psychoses, where the patient is usually able within a week to apply for his own voluntary admission. Summerdale, the annex of Graylingwell Hospital, had 104 such admissions; 8 left at the expiration of the urgency order, 80 continued as voluntary patients, and only in 16 cases was it necessary to proceed with full certification.

In most continental countries judicial authorities do not participate at all in the admission of patients. If a person is unwilling to enter the hospital, the police can assist but the hospital director decides whether the patient can be kept against his will. There exist, of course, several ways of appeal. The different attitude on the part of the patients and the relatives is well illustrated by the fact that in the Swiss Kanton of Berne of 2,672 patients in 1954, only in 11 cases discharge by way of appeal to a supervising authority was requested by patients or relatives. In Germany, where the situation had been equally liberal before the war, the distrust toward mental hospitals, caused by the events during the Nazi regime, led to some discussion whether the American method of court certification should be adopted, but practically all psychiatrists oppose it. In most countries psychiatric departments of universities serve as admission hospitals. In Italy a middle-of-the-road solution is still based on a 50-year-old law. According to this a patient is admitted on a note from a doctor through the police for 30 days; he can then be discharged and readmitted; but if he is not improving he has to be court-committed. Even this law is about to be abolished.

Admission and discharge rates in all European hospitals are extremely high. While up to 80% of the available beds are taken up by chronic patients, the remaining 20% available for active treatment patients provide for an amazing turnover. In England admissions have doubled during the last 10 years, but discharges have increased likewise, and, although most hospitals are just as overcrowded as ours, they managed without construction of new buildings. The average length of stay in an English institution at the time of discharge is a little over 2 months, and 90% of those discharged leave the hospital within the first year.

The admission rate of an average European mental hospital is almost 70% of its bed capacity. In Graylingwell Hospital with 1,123 patients, 788 or 68% were new admissions; this is almost identical with the admission rate of a German institution in Hamburg chosen at random, and close to the rate of 70% to 75% in the 3 mental hospitals of the Swiss Kanton Berne. In American institutions the admission rate lies only between 20% and 25% of the bed capacity. It should be pointed out that the figure of 70% refers to mental institutions comparable to our state hospitals. An institution functioning as a teaching hospital like Zurich-Burghoelzli has admission rates twice its bed capacity, but a visit to the second mental hospital in the Kanton Zurich, the Rheinau, showed a correspondingly lower admission rate of only 25%, thus giving again the usual rate of 70% to 80% for the whole area. As an example of a teaching hospital which, at the same time, is the only institution of that area, figures from the Friedmatt in Basle may be quoted: this 544-bed institution handled 999 admissions; 868 patients could be discharged and the remaining beds were freed by death and transfers to an old age home.

The large turnover is made possible by an extremely liberal discharge policy. A different attitude by the general public and the press necessarily removes the fear on the part of the hospital director to be blamed for unfortunate events that might occur with discharged patients. Readmission rates, of

course, are high in hospitals with a policy of early discharge. They may run up to 40%, and, in one of the best English hospitals I visited, were doubled within the last 7 years. This is mostly explained by the fact that relatives take patients out too soon, even against advice, but Dr. Maclay, in charge of all mental hospitals in England and Wales, pointed out to me that the advantages of good will by the population surpass the disadvantages. European admission diagnoses hardly differ from ours. The ratio of the major psychoses such as schizophrenia is apparently the same everywhere, and there is a general increase in the old age group. Differences noted were that in England more neurotics apply for admission to the better-accepted mental hospitals, and that in Switzerland more alcoholics seek admission.

European hospitals work under incomparably better conditions than ours. For one, there is no shortage of well-trained psychiatrists. Private practice is no incentive for doctors trained in psychiatry. The English hospitals benefited from the National Health Act because prominent practicing psychiatrists are now paid for consultations in mental institutions. Thus, both full-time and part-time work in mental institutions became more desirable. Most hospital directors in Europe did not come up through the ranks of a mental hospital but worked in psychiatric departments of a university hospital. This promotes clinical research, which is very common, while the need for basic science research centers in institutions is sometimes questioned. Young psychiatrists benefit from the university background of their chiefs. They are far more independent than in our hospitals. Decisions on treatment and discharges are mostly left to their judgment. Therapeutic problems are often handled quite differently by different psychiatrists in the same hospital. The ratio between physicians and patients is not very high. In the 1,050-bed Warlingham Park Hospital, 12 doctors take care of 850 admissions and 11,500 attendances in outpatient clinics. Figures elsewhere are similar. Their administrative duties are minimal. This includes the superintendent of the hospital, who can delegate much more administrative work to the "secretary" or steward and can, therefore, concentrate on medical problems. Even in England with a central "Board of Control" the freedom given the individual superintendent is amazing. The visitor to mental hospitals in various countries is left with the impression that their quality does not depend on any particular type of central organization but on the personal initiative of the psychiatrist-in-charge.

Psychiatric nurses and attendants are well trained and carefully selected. Comparing their ratio here and abroad would be meaningless because in the many wards where all patients are working, nurses are not needed during the day, and some good wards are entirely without night supervision. Employment in institutions is considered more desirable than here. In Switzerland attendants with some kind of professional training are preferred because they can contribute their technical skill to the work therapy program, and also because it is felt that people with professional training have already shown a certain steadiness which helps to exclude psychopaths and undesirable elements. The duties of an attendant are more those of guidance than of supervision. Groups of 8 to 10 difficult patients are sometimes assigned to the same nurse for all their activities. The nursing staff in some English hospitals has its own club for social and sports activities which is open all day, and which seems to be a valuable means of keeping employees. The stability of the nursing staff is also illustrated by figures from a rural institution in Muensingen, Switzerland, where from a staff of 257 in 1953 not one male attendant left, while 26 female attendants left probably because of marriage or childbearing. Attendants are mostly trained on the job and have to pass an examination. In Graylingwell Hospital, Chichester, I was told that the nurses-patient ratio is 1:4; 80% were trained or in training, a few worked as orderlies. English hospitals also employ part-time nurses.

There are only few social workers in continental institutions. They are more numerous in England, where the average 1,000-bed hospital employs about 3 social workers. Their duties include taking social histories of newly admitted patients, thereby estab-

lishing useful contact with the family which is continued after the patient's discharge by the same social workers. They also take an active part in the social clubs for patients which are discussed later. Occupational therapy as a profession is less common. Psychologists are little in evidence; again there are more in England than on the continent, where their work is limited to mental defectives. A special type of teachers trained in abnormal psychology, the so-called *Heilpaedagogen*, particularly in Germany, is engaged in the teaching of abnormal children. Psychotherapy by psychologists, although common in extramural psychiatry, has not been encountered in institutions.

Active treatment is applied everywhere. Neither the somatic treatments nor formal psychotherapy are the "number-one" approach. The treatment applicable—and actually applied—to every patient, young or old, acute or chronic, is "work therapy" which has largely replaced the former unproductive type of occupational therapy. This deep belief in work therapy is common to all European institutional psychiatrists. While in England the emphasis is more on social and recreational activities, continental psychiatry emphasizes actual work in and outside of the institution. This philosophy was introduced by and is still identified with a German, Herman Simon, of Guetersloh, as work therapy. In another Westphalian institution, Lengerich, where apart from some decrepit patients, 98% to 99% are working, Merguet calls it now socio-therapy, identical with the English term social therapy. Its basic philosophy is the need for maintaining initiative and social adaptability in the patient. Likewise in Swiss institutions I found even the worst wards empty during the day, and in Rheinau (Dr. Binder) with a very chronic patient material the ward physician apologized for the dull atmosphere, when I visited on a Sunday afternoon on which the patients were inactive. The Swiss see the main value of the new tranquillizing drugs chlorpromazine and reserpine in the reduction of non-working patients, so that, for instance, in one disturbed ward of 90 male patients only 1 or 2 are not working compared with 20 or 30 previously. Work consists of any type of occupation in and for the hospital, and it may be added that no complaints of exploitation of patients are feared. The public has been made to understand with the help of the press, that the mental patient is in urgent need of occupation and work. The industry cooperates in employing discharged mental patients, and in England the Ministry of Labour gives full assistance to the resettlement of the mentally disabled.

In England the most disturbed patients are included in recreational and social therapy. In Netherne Hospital I saw the 12 worst female patients who had been too bad to go to the movies, but for whom a special outing had been arranged. They had been sent on a picnic with 2 nurses, and it was felt that their behavior had improved considerably after their return to the hospital. They had not received any drugs or electroshock therapy for some time, and the director, Dr. Freudenberg, although internationally known for his work in shock therapy, feels that such efforts can do away with most of the somatic treatments. An especially cherished peculiarity of English hospitals are social clubs. They are not limited to neuroses centres like Belmont Park, which will not be discussed in this presentation limited to institutions. The patients who are working during the day are encouraged to join various social and recreational activities after 5 p.m. Social clubs have an important part in the life of discharged patients who are free to visit the weekly meetings. Some activities such as outings are even organized and paid for by the patients themselves. One staff physician and a social worker are usually present. They do not see patients individually, but, on the basis of their observations, often refer discharged patients to the clinic. These social clubs help the discharged patient in his frequent difficulties to make social contacts, and at the same time they are an unobstrusive aid in after-care.

Somatic treatment is often considered as being only an adjunct to the entire management of the patient. Some hospitals were able to show a considerable increase in discharges already with the introduction of work therapy prior to the shock era. Yet shock treatments are applied intensively in all acute cases, while in chronic cases there is more reliance on work therapy. Psycho-

surgery continues to have an important place in the treatment of psychotic patients in England more than on the continent. The tranquillizing drugs, while increasing the number of working patients, did not seem to increase the discharge rate in European hospitals with their already amazingly high discharge rates. Formal psychotherapy for psychotic patients has not been encountered anywhere except in Burghoelzli. In Graylingwell, Chichester, a psychoanalyst is assigned to the hospital, but apparently is busy mostly with the steadily rising number of neurotic patients admitted to English hospitals. Her task is the psychoanalytical treatment of some long-term cases, some short-term cases, consultation with other members of the staff, and the holding of seminars. The over-all impression is one of great therapeutic optimism, and most hospital directors believe that the majority of mental disorders is curable if promptly treated.

There is a trend to avoid special wards. In some hospitals even the separation of quiet and disturbed patients is avoided because it is felt that difficult patients benefit from the company of good patients who can be taught to assist the sicker ones. Special wards for active treatment easily lead to therapeutic nihilism in those wards to which the treatment failures are sent. Therefore, there seems to be a tendency to do away with special treatment wards in favor of active treatment being applied in all wards. Also special admission wards are no longer common to all hospitals. In Netherne, for instance, the newly admitted patient comes to an admission room, and from here he is immediately sent to a ward with patients of the same age group. A senior psychiatrist is always at hand for new admissions, and in case of suicidal danger even a junior physician can give electroshock treatment immediately. Early treatment is characteristic for most hospitals with no staff conferences necessary to decide on the treatment, although the director of the smaller European hospital can keep informed more easily about individual patients. There are some provisions to review the treatment situation before a board or quorum after a certain period of unsuccessful treatment.

One of the most amazing features is the quiet atmosphere in most so-called disturbed or tough wards. Cheerful and homelike appearance due to drapes, rugs, pictures and flowers in all, including the disturbed wards, is most impressive, and, according to staff members, most helpful in the prevention of regressive symptoms. The well-known signs of deterioration in chronic schizophrenics are no longer in evidence. Most European hospital directors, who emphasize the friendly and hopeful atmosphere which is so characteristic of their hospitals, rightly resented the description of mental hospitals as "snake pits."

Every effort is made to maintain in the patient the feeling of personal responsibility and dignity. Clothes, even when furnished by the hospital, should have a personal touch. Patients are allowed to bring personal property, and in many institutions they are permitted to wear rings and watches. Lockers with keys are entrusted to the patients. The sexes mix much more freely because it is felt that manners are better preserved in the presence of the opposite sex. In one hospital places in the dining room are being changed every week to avoid the formation of isolated groups. Such small things are considered important in the over-all management. Life in an institution is kept as close to home life as possible. Visits at home are encouraged wherever possible. In a Swiss institution of 500 patients 300 go home every weekend and, at carnival time, for several days. This continued contact with the family unquestionably improves the patient's chances for a return to the community.

Restraint has been abolished long ago in all European hospitals. Straight jackets are shown in some museums of university institutes. Also chemical restraint is said to be made unnecessary by appropriate management, and the 1,200-bed hospital Lengerich was able to cut down sedation to 10 individual doses a day. In England this change is often attributed to the abolishment of closed wards. In Warlingham Park Hospital the last wards were recently opened. This extreme attitude is not shared by most other hospital directors. In the frequently mentioned Graylingwell Hospital, 6 of 26 wards are locked. There is no doubt that open wards diminish the aggressive tend-

encies of a patient, and in one place I heard the statement that open wards make the tranquillizing drugs superfluous. In Switzerland more wards are closed, but many patients are permitted to walk on the hospital grounds without supervision. It is my impression that the open ward as such is not an indispensable feature for favorable therapeutic results in a hospital.

Little can be said about architectural planning of mental hospitals in countries where no new hospitals are being built. Comparatively new, pre-war Runwell Hospital near London consists of small cottages with porches, onto which the beds of bed-ridden patients can be moved. Most impressive is a new building for disturbed patients in Basle-Friedmatt, built according to the directions of the psychiatrists Staehelin and Kielholz. The whole building is soundproofed and air-conditioned. Not more than 2 patients are in one room. The window panes are made of plexiglass. Each room has a toilet to discourage wetting and soiling. An intricate alarm system for the nurses is one among many interesting features of this amazing structure. Most European hospitals had to limit themselves to redecorating and refurnishing, and to small changes to make monasteries and old Victorian halls into real homes for psychiatric patients.

A great problem everywhere is how to avoid new constructions in spite of the steady increase of patients in the old-age group. In England, in the year 1952, almost 20% of all admissions and 28.8% of all mental hospital inmates were over 65 years old. The corresponding figures for 1938 were only 12.3% for admissions and 17.5% of the total hospital population. Figures from other countries are similar. Measures to cope with this problem differ very little from those recommended in this country, but again the greater cooperation on the part of the general population and less rigid administrative policies ease the situation. Emphasis is on the possbility of treating many psychiatric syndromes in old patients with the same methods applied successfully in the younger age groups. Pilot studies in several hospitals confirmed the frequency of depressions in old age, and in one hospital 38% of the old-age population could be discharged. Chlorpromazine and reserpine are considered a great help in overcoming the short-lasting disturbed psychotic episodes which frequently lead to unnecessary permanent hospitalization. Special geriatric departments in general hospitals have a psychiatric unit providing active treatment and thus preventing many admissions to a mental hospital. Day hospitals, where senile patients can be kept and treated during the day and return to their families for the night contribute to the relief of pressure on mental hospitals. Domiciliary visits by the mental hospital staff also keep many patients outside of institutions. Special annexes for old patients who do not require full hospital treatment are planned for mental hospitals in England. An unusual approach to this problem was seen at Warlingham Park Hospital which established a self-containing unit for old people in a beautiful castle at a considerable distance from the hospital. The purchase price of such estates is low and the cost in this old-age annex was only £3.10.0 weekly compared with over £5 for other patients.

It is accepted procedure to keep senile patients mobile, occupied, and interested. On the physical side this prevents bed sores and contracted limbs and, on the mental side, demented behavior. It is regarded as most important to screen senile patients and, wherever possible, to treat them in general hospitals or at home. If they have to be admitted, old age homes are preferable but should be visited regularly by the mental hospital staff. There is agreement that such measures can reduce considerably admissions of seniles to mental hospitals. It is being realized everywhere that this problem can be solved only by the joint efforts of the mental hospital, geriatric units in general hospitals, old age homes and welfare agencies.

Mental institutions in such countries as England and Switzerland are not limited to inpatients but provide active outpatient treatment. Any statistical comparison must take into consideration that many patients who, here, would be committed to a mental hospital, in Europe never reach the hospital because they are treated as outpatients. This includes, for instance, many depressions who receive ambulatory electroshock treatment

in one of several outpatient clinics of the mental institution. Dr. Rees from Warlingham Park Hospital estimates that his doctors spend one-third of their time with outpatient work. General hospitals established psychiatric wards which are staffed by the mental hospital. Also on the continent this development originated from the mental hospital, and recently Burghoelzli opened an observation ward in the general hospital in Zurich. English clinics, staffed by the mental hospital but run by local authorities, also serve as aftercare clinics, and with their facilities for ambulatory treatment prevent many readmissions.

This paper deals with institutions but the intensive outpatient work in general and teaching hospitals should at least be mentioned as, for instance, St. Thomas Hospital in London which has only 14 psychiatric beds but 16,747 outpatient attendances. Other psychiatric clinics are run on a district level and unrelated to the mental hospital as, for instance, in Amsterdam and in Berlin, where aftercare and rehabilitation of discharged patients are provided together with all other psychiatric needs of the area.

In the work of community clinics adult psychiatry is more stressed than in the United States. I was given a figure of 400 adult clinics in England and Wales as compared with only 200 child-guidance clinics. It has been shown that the establishment of any clinic for adults helps to diminish the case load of the mental hospital in that area. There are also many other means used to unburden the hospitals. While boarding out does not seem to play a major part in most countries, the mental hospital in Aarhus, Denmark, is said to supervise the same number of patients boarded out as it cares for as inpatients. Another way to ease the institutional case load is a sort of work camp for mental patients in defect remissions like the Buergerspitals-Lager in Basle, where patients are doing work therapy and are supervised by a matron. Day hospitals are still in the experimental stage. Some differ little from outpatient clinics, others concentrate on work therapy. The Swiss hospital Friedmatt in Basle also has night patients who work in the city during the day, but still live in the hospital, an arrangement which in some cases is a transition before discharge, in others is continued for years. In this hospital the day patients are mostly schizophrenics in defect remission, who would be unable to compete on the general labor market but who work in the hospital. The same applies for the alcoholics who work in the hospital and also receive their daily antabuse dose there. In England domiciliary visits by the senior staff of the mental hospital are considered an important means to avoid hospitalization, and, at the same time, to strengthen the contact between mental hospital and community.

This paper deals only with the advances in European mental hospitals because only acquaintance with these can stimulate our own endeavors in this field. It would be wrong, however, to believe that all hospitals operate on an equally high level. Their quality varies widely between countries, and even in the same country there are great differences. In England, where in spite of the nationalization of all health facilities mental hospital administration is largely decentralized and almost exclusively left to regional boards, there are backward hospitals. Recently, they were bitterly attacked in a newspaper series which, however, was followed by another series about the great strides made in most hospitals. The transition from asylums for custodial care to hospitals and, beyond this, to therapeutic communities is nowhere completed.

The importance of public support for mental hospitals has been stressed repeatedly. In all European institutions psychiatrists seem to be working under better conditions in this respect than they are here. The greatest awareness of the need for good public relations exists undoubtedly in England, where I repeatedly met organized parties from civic groups who visited the hospital including the least desirable wards. Such visits help to remove prejudices against the hospitals and make the people more willing to accept discharged patients back into the community. One director pointed out to me that visits by lay groups may even encourage the sons and daughters of such visitors to enter the psychiatric nursing profession. In England good public relations are most important because the funds for the hospital

in a particular area are granted by regional hospital boards. Therefore, every effort is made to make the people aware of their responsibility for the mentally ill. What has already been achieved is best expressed in an enviable statement which Dr. Carse, Superintendent of Graylingwell Hospital, was able to make in an annual report and with which I want to close:

> Psychiatry and our mental hospitals have emerged from the age when they were viewed with suspicion, fear and distrust because most people already accept the fact that a psychiatric patient is much the same as any other patient, someone suffering from a definite illness which, fortunately, usually responds to specialized treatment when given promptly.

DISCUSSION

Z. M. Lebensohn, M. D. (Washington, D. C.).—At this critical time in American psychiatry there is a greater need than ever before to re-examine our entire hospital treatment program. In doing this I believe we have much to learn from studying European mental hospitals and their methods. The author has done us all a great service by supplying us with this compact, critical survey of present trends in European hospital psychiatry. My own observations, based on visits to several hospitals in England, Norway, Holland, and France in the autumn of 1955, are in accord with Dr. Kalinowsky's findings. Therefore, I wish to address myself briefly to another aspect of the problem which applies to us in this country.

I cannot refrain from noting that neither the author of this fine paper nor his discussants are hospital psychiatrists in the operational sense of that term. One cannot underestimate the great value of the mental stimulation—the cross-fertilization of new ideas—that can be derived from a period of study in a European hospital. But it is really the ***hospital psychiatrist*** who should have made this trip and written this paper. I can think of no wiser expenditure of Foundation funds than to set up a series of travelling scholarships for qualified and deserving hospital superintendents, clinical directors, or staff members, providing them with 3 to 6 months' study abroad in some of the hospitals described in this paper. The rewards in improved hospital treatment methods and broadened approach would be immeasurable. I trust the Foundations are listening.

CLINICAL NOTES

RECURRENT THORAZINE INDUCED AGRANULOCYTOSIS

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At least 50 cases of agranulocytosis occurring during treatment with chlorpromazine (Thorazine) have been reported. That this should occur from time to time is not surprising in view of the chemical structure of this drug. Most of the reported cases have occurred within 1 or 2 months after the beginning of treatment. With few exceptions the reported cases have consisted of female patients. The writer is aware of only 2 male cases, including one previously reported by the author.

Reports of agranulocytosis following treatment with chlorpromazine have been reported by Munch-Peterson (1954), Lomas (1954), Pollack (1955) 1 case among 500 patients, Tasker (1955); Boleman (1955), Prokopowycz (1955), and Shapiro (1955). Giacobini and Lassenius (1954) reported 1 case among 147 patients treated, Goldman (1955) 4 cases in the treatment of about 1,000 patients, Barsa and Kline (1955) 2 cases among 300 patients. Lomas, Boardman and Markowe (1955) refer to 7 further unpublished cases of arganulocytosis following treatment with chlorpromazine. Other reports have been made by Ayd, Adams, Corti, Hobson, Tillim and Stone. Yules reported a case of agranulocytosis occurring in a 78-year-old woman which did not recur on retreatment.

As far as I can ascertain, there have been no cases reported in the literature similar to the present one. In our series of over 2,000 chlorpromazine-treated patients, there have been only 2 cases of agranulocytosis.

T. H. an 82-year-old woman was admitted to the Strong Memorial Hospital on July 9, 1955. About 1 year previously she began to exhibit memory loss and disorientation, with restlessness and excitement. Two months previously she had been placed on Thorazine by her family doctor (exact dosage unknown). On July 6, she became delirious, stuporous, and developed a fever. She appeared acutely ill. There was marked ulceration of her throat, with erythema of the posterior portions of the palate, the uvula and the tonsillar fossae. A diagnosis of Thorazine-induced agranulocytosis was made on the basis of a blood count on admission which showed only 700 white cells (almost entirely lymphocytes). The following day the white count fell to 425 and counts on the next 2 days showed white blood counts of 550 and 700. A report of the bone marrow obtained from a sternal puncture on July 11 was reported as follows:

Peripheral blood showed evidence of marked leucocytopenia. Differential smear showed only lymphocytes with occasional reaction forms and no young forms. Erythrocytes are normocytic and the majority are normochromic, with slight anisocytosis, and slight polychromatophilia. Platelets are of normal morphology and normal in number.

The bone marrow was hypocellular and obviously was markedly dilated with peripheral blood. Megakaryocytes appear to be mature and in the lower limits of normal number. Erythroid series was markedly hypoplastic with a few late stages seen. A very rare basophilic and prenormoblast form is found. It is normoblastic. Myeloid series—a very rare young neutrophil form is found along the edge of the smear. A very rare blast form was seen on searching one smear. Differential on 50 cells: 80% lymph, 20% monos. Lymphocytes display much pleomorphism—many showing toxic characteristics. No immaturity was noted. A rare plasm cell is present. The smear is suggestive of hypoplasia of the myeloid elements.

The patient was treated with massive doses of penicillin and streptomycin, and parenteral fluids. She became afebrile after 4 days and the mouth lesions cleared. The white blood count increased and on July 14 was reported as 1,600. The white count on July 18 was reported as 7,500 and on the 20th as 9,700, on the 21st as 12,800, and on the 22nd as 14,000. The count gradually returned to a normal level. A blood marrow examination from another sternal puncture taken 10 days after the acute onset indicated "a remarkable degree of recovery of bone marrow function, especially in the myeloid series and suggests that the patient had some overshoot." The patient made an uneventful recovery from this acute illness. She was then given an oral test dose of Thorazine, 10 mg. on one day and 25 mg. on the next day, without any subsequent change in her blood picture. She was transferred to the Rochester State Hospital on August 18, 1955, because of the continuation of her disturbed behavior. At that time the physicians had no knowledge of her previous agranulocytosis. At this hospital she continued to be extremely noisy. On January 10, 1956, she was given 200 mg. of Thorazine by mouth and this was repeated daily

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for the next 11 days. At first the patient became quiet and cooperative, and the drug was finally discontinued because patient's behavior seemed improved. During this period of medication no change was noted in her physical state. As time went on she gradually became noisy again and on June 21, 1956, she was placed on 50 mg. of Thorazine twice daily. She became quieter but still had periods of excitement and marked confusion. On July 4, she complained of dizziness, staggered about and seemed very drowsy. Her temperature was 103° and she became increasingly drowsy and finally almost stuporous. She appeared dehydrated, throat was inflamed without, however, any petechiae, and moderate exudate. There were no other abnormal new physical findings. She was placed on high doses of antibiotics such as penicillin, streptomycin, and terramycin. Her initial white count was 1,200 with no granulated leucocytes and 97% lymphocytes and 3% large monocytes. Plateletes were slightly decreased; Thorazine was discontinued. On July 6 white count was 2,000; on July 9 it was 1,200; on July 10, 1,400; on July 11, 1,200; on July 12, 1,100; on July 13, 1,200; on July 16, 3,100; on July 17, 3,400; on July 18, 3,900; on July 19, 4,400; on July 20, 5,700 and on July 25, 8,700. Following this the patient made an uneventful recovery to her previous state.

This case is of interest because it is probably the first report of recurrence of agranulocytosis in a patient under chlorpromazine medication. Yules reported a 78-year-old woman who had developed a similar agranulocytosis, who on retreatment with chlorpromazine failed to reproduce "a leukopenic reaction or frank agranulocytosis."

The mechanisms responsible for the production of agranulocytosis in certain patients are still not clear. Further study and further reports are necessary before the complex etiology of this rare complication of chlorpromazine therapy can be elaborated.

FORENSIC NOTES

THE MINNESOTA SUPREME COURT EMPLOYS THE DURHAM TEST

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The patient presented a fairly typical history of paranoid schizophrenia. He had always been shy and sensitive. He left school in the ninth grade, feeling that others were making fun of his appearance. He worked as a farm laborer, mostly on his father's farm. During the war he served 2 years in the navy; his service was terminated by what was apparently a short paranoid psychotic episode. In 1949 (age 37) he married a divorcée and settled on a farm. Soon thereafter he began to express paranoid ideas concerning his wife. On several occasions he sought the sheriff's aid because of his wife's alleged infidelity. In one instance he hired detectives to trail her; after this he was sure that she was trying to poison him. In June 1951 he made a single visit to the medical clinic at the University of Minnesota Hospitals. A tentative diagnosis of a paranoid psychosis was made and he was referred to the psychiatric clinic but he failed to return, relating to his sister that the doctors "laughed" at him and thought of him as "nuts." In June 1952, while his wife was sleeping, the patient shot and killed her with a rifle. He then turned himself over to the authorities, who sent him to the University Hospitals for psychiatric study.

Upon direct examination he was quiet and sad-appearing, but cooperative. He indicated that he understood what had taken place, and he asked to be shot before a firing squad. He further indicated that the F.B.I. had been watching him for years and that on occasion he had heard voices accusing him of immoral behavior. Our report to the court indicated that the patient was clearly psychotic, that in our opinion he was legally insane.

In November 1952 the district court found the defendant to be "insane with homicidal tendencies" and therefore incapable of standing trial. He was committed to the state asylum for the dangerously insane.

In March 1955, a different trial court in a civil action concluded that the defendant was legally sane at the time he killed his wife. This civil litigation involved the question whether or not a killer can benefit from his act by the transmission of property from the deceased. The action was taken on behalf of relatives who were contesting the disposition of the decedent's estate. At the trial the defendant was not re-examined, but a neuropsychiatrist, after reviewing a transcript of the criminal proceedings, testified that the defendant "knew the difference between right and wrong and had full realization of its legal consequences."

This decision was reversed by the Supreme Court of Minnesota(1). In doing so the Supreme Court used the wording of the Durham(2) or "product of disease" test:

> The fact that [he] committed the act knowing it was wrong with full realization of its consequences should not be considered in a vacuum apart from the disease which produced the act. We feel that the better rule to be applied to the case before us is that the slayer will not be barred from taking the property where his unlawful act was the product of mental disease. In light of the present-day medical knowledge of the nature of mental diseases, it is not realistic to apply the arbitrary right-and-wrong test to the facts in this case.
>
> The record is replete with evidence supporting both doctors' testimony that the defendant was afflicted with a serious mental disease at the time when he killed his wife, and we find that there was a sufficient causal relation between the disease and the killing to warrant a finding that it was the defendant's insanity and not his own conscious act which caused the death of his wife. Therefore, the equitable principle that one should not be permitted to profit by his own wrong does not apply to the facts in this case and a constructive trust will not be imposed.

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It should be noted that the right-wrong test is by this case abandoned only in a limited area: a noncriminal case having to do with inheritance. To this restricted extent the judges were free to change the law. The question of criminal responsibility in Minnesota is still controlled by the M'Naghten rules (Minnesota Statutes, section 610.10) by force of legislation adopting them. Therefore a complete movement away from M'Naghten must await legislative action.

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HISTORICAL NOTES

EDWARD MEAD AND THE SECOND AMERICAN PSYCHIATRIC JOURNAL

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Although psychiatric periodical literature had its beginning in the German "psychologico-philosophical" periodicals of the late eighteenth century which were followed by a number of short-lived journals edited by doctors of medicine, it was not until the fifth decade of the nineteenth century that the first psychiatric journals were established that have continued to the present time(1). The first psychiatric periodical in English was published in July 1844 at Utica, New York, by Dr. Amariah Brigham as the *American Journal of Insanity* which continues today as the *American Journal of Psychiatry*(2). Nine years later Dr. Edward Mead founded the second American psychiatric periodical, the *American Psychological Journal*.

Edward Mead was born in Leeds, England, on March 21, 1819, the second of 5 children (3). His family came to the United States when he was 12 and apparently settled in Illinois. He began the study of medicine under Dr. Robert Thompson of Columbus, Ohio, in 1838. As this was the same year that the Lunatic Asylum of Ohio was founded in Columbus, it may be reasonable to suppose that current interest in the mentally ill started Mead in the direction of his future career. His medical studies were interrupted by a period of ill health, during which time he traveled through the south and developed definite antislavery views. He continued his training at the Medical College of Ohio in Cincinnati, from which he graduated in 1841. Following the custom of the times he continued his study of medicine abroad, spending several months in England, Ireland and France. He returned to Cincinnati, but at the urging of relatives, soon moved to the outskirts of Chicago and probably settled at St. Charles. There in 1842 he married Minerva Baird, who bore him 7 children. She died in 1859. He remarried in 1860 and had 2 children by his second wife. His medical practice grew to be extensive but his interest turned to the pitiful state of the "insane" in the area.

Some of the local citizens had been working for the creation of an insane asylum since 1829. Mead actively joined this movement and is said to have done the greater share of the work, writing some 700 letters over a 3-year period in the interest of establishing an asylum. On November 3, 1845, he delivered "An Appeal on Behalf of the Insane" in the Presbyterian church in Jackson, Illinois(4), wherein he stressed the treatment role of the hospital. He next successfully proposed at the May 19, 1846, Rock River Medical Society meeting that a committee be formed to study the status of the insane in Illinois and subsequently served as a member(5). Dorothea Dix delivered her dramatic memorial to the Illinois legislature in 1847(6) and as a result received most of the credit for establishing the Illinois State Hospital for the Insane at Jacksonville(7, 8). On the first draft of the hospital bill passed by the legislature, Mead was appointed as one of the 3 medical trustees. They were all dropped subsequently on the grounds "that the parent college [the medical department of Illinois College to which they belonged] was managed by Yankees and Presbyterians" (9). The opposition, who assumed that Mead would be the most likely one to be appointed superintendent, opposed him on the grounds that a small man (he stood 5 feet 4 inches) could not manage the lunatics. Although he declined the candidacy for the position, his opponents were not successful in being selected. Dr. J. M. Higgins was appointed superintendent in April 1848 and was in charge when the hospital opened 3 years later.

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During these busy years, Mead was also devoting much energy to another of his interests, teaching. He was professor of materia medica, therapeutics, and pathologic anatomy at the Franklin Medical College at Saint Charles. This medical school, which opened in 1842, was the first in Illinois and continued until 1849 when Dean G. W. Richards, the founder, was shot by a member of an angry populace for suspected grave robbery(10). In 1844 Mead gave a report on medical education to the Illinois medical convention. He served as professor of materia medica and therapeutics at the medical department of Illinois College for 1 year, resigning in 1847. This school was also disbanded because of its unpopularity in the community(11). In 1846 he attended the National Medical Convention in New York as the only delegate from Illinois and served on the committee formed to prepare a report on medical education which was given the following year(12).

In 1847 he threw himself wholeheartedly into psychiatry. He gave up his practice and moved to Chicago where in August he opened the first private hospital for the insane in Illinois(13). By December 23, 1851, he had treated 139 patients and reported 63 cured and 13 dead. He admitted them for a period of not less than 3 months and at a basic rate of $4.00 per week or $10.00 if an attendant was necessary(14). In 1851 his establishment was completely destroyed after a patient set fire to his buildings.

Dr. Mead was appointed to the chair of obstetrics and diseases of women and children at the newly founded Cincinnati College of Medicine and Surgery in October 1851 (15) and gave the valedictory address to the students the following spring(16). In October 1852, he opened the Cincinnati Retreat for the Insane(17). He continued to teach obstetrics during the winter but resigned at the end of the term because of ill health. He remained on the staff of the college through the creation of a new chair, that of insanity and forensic medicine(18). In accepting this appointment, he appears to have become the second professor of psychiatry in the country, the first being Dr. Samuel M. Smith who had been appointed to a similar chair at Willoughby University, Columbus, Ohio, in 1847 (19). In the autumn of 1853 he resigned from the medical school as his ideals were in conflict with policies of the president, the founder of the college.

It must have been in the autumn of 1852 while giving his preliminary lectures on insanity and establishing his second private asylum that he decided to found the *American Psychological Journal*. In the first issue dated January, 1853, he gives his concept of the journal:

> The range of discussion will embrace Mental and Moral Philosophy, Psychology proper, the numerous forms of Mental Pathology, with their legal relations and the various affections of the Nervous Systems.

Insanity was to be the principle topic. He stressed that

> . . . a wider dissemination of knowledge on these subjects [mental and moral training] would render much less efficient the known cause of insanity.

He goes on to speak of the British and French journals and also of the *American Journal of Insanity*.

> What the two former have accomplished in Europe, and the last in the Eastern portion of the United States, we hope to accomplish for the West.

He planned to be practical but to leave space for

> . . . philosophical discussion of well grounded theories. . . . We shall aim at perfection.

His intentions were good and his hopes high but this rare little journal lasted through only the 6 issues of the first year. Its beginning must have been faltering as in the second issue he apologizes for its tardiness which resulted from an illness of the editor and reassures his readers that publication will continue to the end of the year.

A brief consideration of the contents is in order. As was the custom of the day, the large part of the journal was taken up with editorial notices, book reviews, and extracts from other journals. The original communications consisted of "Moral Insanity and its Legal Relations" by L. R. Johnson, M.D., who commented that he was presenting nothing original and that "as a profession, we are sometimes reproached with being men of theories rather than facts"(21); "Asylums for Colored Persons," by John M. Galt, which was the product of a committee of the

Association of the Medical Superintendents of American Institutions for the Insane and apparently not published elsewhere; and Mead's "Appeal on Behalf of the Insane" which had been given in 1845.

In the last issue (November 1853) Mead wrote the following:

> A hint to the Trustees of Insane Asylums. We would respectfully suggest that all candidates for medical appointments in Institutions for the treatment for insanity, should be required to undergo examination before the Association of Superintendents of American Institutions for the Insane, and to present a certificate of qualification from that body.

Mead had long been bothered by the politics involved in selection of superintendents and felt this was a way of solving the problem. His suggestion long lay dormant and only became a reality nearly 100 years later when a committee on Qualifications and Training Standards for Mental Hospital Administrators was formed in The American Psychiatric Association in 1951(22).

Information on the remainder of Mead's life is less complete. He was active in the Ohio medical societies and in 1857 gave a paper on "Moral Insanity" to the Ohio State Medical Society(23). In this he discussed the difficulty of diagnosis and stated that "basing a definition upon an aggregate of symptoms" would create even further problems. It appears that he gave a course of lectures on insanity at the Medical College of Ohio in 1858. In 1860 he unsuccessfully applied for the superintendency of the Alabama Insane Hospital and complained in a letter to Dr. Thomas S. Kirkbride that his application had mysteriously disappeared(24).

He closed his Cincinnati Retreat in 1869 and we next find him opening a private hospital in Winchester, Massachusetts, in 1872 followed by another at Roxbury in 1873 which he ran until his death(25). He died in 1883 when the vessel on which he was vacationing sank off the coast of the Azores.

Although one of the lesser figures in early American psychiatry, Dr. Edward Mead nevertheless made many real contributions: to the many patients he helped in the 4 private hospitals he founded and presided over, to the people of Illinois in his efforts to procure their first state psychiatric hospital, to the early western medical schools and the students thereof, and as the second professor of psychiatry in this country. It was to psychiatry that he devoted his life and in the furtherance of this field, started the second American psychiatric journal. That it failed after a year does not detract from our admiration of his intent and endeavor.

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CASE REPORTS

ECT AS A LIFE-SAVING PROCEDURE IN A PATIENT SUFFERING FROM DIABETES MELLITUS, UNCONTROLLABLE, DUE TO A PARANOID PSYCHOSIS

A. LEONARD ABRAMS, M.D., AND DAVID J. IMPASTATO, M.D.[1]
NEW YORK CITY

Electroconvulsivetherapy (ECT) has been used as a life-saving procedure in various medical conditions in which the patients, because of a coexistent psychosis, suffered from hyperthermia due to either dehydration or uncontrolled hyperactivity, marked weight loss from refusal of food, ineffective medical treatment from refusal of medication, etc. In our review of the literature, we have not encountered a report describing ECT as a life-saving procedure in diabetes. We therefore believe the following report to be of interest.

S. G., a 63-year-old white male, was admitted to the psychiatric division of Bellevue Hospital with a diagnosis of psychotic depressive reaction with paranoid features and uncontrolled diabetes mellitus. He had been depressed for 2 months with episodes of agitation, self-induced starvation, and paranoid ideas. He had a mild diabetes, usually controlled with 10 units of regular insulin and 20 units of protamine zinc insulin daily. Two weeks prior to admission, he refused insulin and food, stating that they were poisons.

When we saw the patient, he was markedly suspicious and expressed paranoid ideas against his brother and his accountant, who he thought were cheating him. He also stated that his wife and the police were trying to do away with him, and he was convinced that he had cancer of the bowels. During the 2 months of his illness, he had lost 40 pounds. He had suffered 3 previous bouts of depression; the last one, 2 years prior to his present admission, lasted 3 months and yielded successfully to ECT. His father had died from cancer of the stomach and his mother and a sister had had depressions.

Physical examination showed evidence of marked weight loss with severe dehydration; temperature of 100°; blood pressure 120/80; 4 plus acetone and glucose in the urine; and blood sugar 165 mg. Gastro-intestinal series was negative. Electrocardiogram showed sinus arrythmia. Mazzine test was negative. X-rays of the thoracic spine showed hypertrophic osteoarthritic changes. X-ray of the chest showed left-sided perihilar fibrosis and calcification.

He was treated for his diabetic ketosis with intravenous fluids and insulin. Three days after admission, although he was out of ketosis, he continued to refuse food, and his diabetes continued in and out of control. His temperature rose to 104° because of cystitis.

Three days after admission, the blood sugar was 148. Because of extreme difficulty in the medical management of this patient the very poor prognosis unless something was done to improve his mental status, ECT was begun with the Reiter Amplitude Modulated Unidirectional Current. After the second treatment the patient began to eat and required no further tube feeding. From this point on his diabetes was easily controlled. He was given a total of 13 ECT's, and at the time of his discharge approximately 4 weeks after ECT was initiated, he was no longer depressed and manifested no further paranoid ideas. During treatment he gained 19 pounds. At present, 3 years after discharge, the patient is well.

This protocol is an illustration of the life-saving effect of ECT in a medical emergency in which the patient's psychiatric condition makes impossible adequate medical and surgical care. The physical condition of such a patient often deteriorates so quickly that, if the mental condition is not quickly alleviated, he will soon die. These circumstances call for a psychiatric remedy that is both decisive and quick. As illustrated by the beneficial effect on the patient recorded in this report, ECT is the treatment of choice of such patients.

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CORRESPONDENCE

PACATAL

Editor, THE AMERICAN JOURNAL OF PSYCHIATRY:

SIR: In July 1955, Volume 112, No. 1, in an article entitled, "Use of Pacatal (N-Methylpiperidyl-(3) Methylphenothiazine) in Psychiatric Patients," Dr. G. M. Jacobs and I described the effects of Pacatal which was a new preparation at that time. The material was supplied to us by a pharmaceutical house direct from the manufacturers in Germany. The side-effects of the drug were so severe we felt that it was too toxic for clinical administration. Later this drug was manufactured by a pharmaceutical house in the United States and in Canada, and the clinical results by competent investigators differed considerably from our own in respect to side-effects. This led us to re-examine our own investigation to attempt to determine the reason for this difference. Upon request we were furnished with a sample of the new material and we sent both the original product and the new material to an independent chemical laboratory for analysis without indicating the reason for our request or identifying either substance. This laboratory report indicated a considerable difference in chemical composition which led us to suspect the original material might have been contaminated or inadequately prepared. A number of isolated instances of the use of the original material elsewhere and here confirmed the toxicity of the first material.

In view of our strongly negative article based on the German materials we felt that we ought to re-examine the product and a supply manufactured in this country was made available to us. We have now used the product manufactured in the United States for approximately 9 months and although it has side-effects (as does any effective medication including those in the psychiatric field) there is evidence that there was something wrong with the batch on which we did our original examination. The drug does appear to be an active one and we believe that clinical investigation should be carried out to determine its usefulness in the treatment of psychiatric patients.

NATHAN S. KLINE, M. D.,
Director of Research,
Rockland State Hospital,
Orangeburg, N. Y.

"NO PSYCHOSIS WITHOUT NEUROSIS"

Editor, THE AMERICAN JOURNAL OF PSYCHIATRY:

SIR: I wish to call your attention to a recent misuse of an old quotation. I am concrened not merely because the erorr appears in our journal but also because it is so frequently misunderstood by students and by members of allied professions.

On page 14 of the July 1956, issue Dr. Arnot, in discussing the fact that some neuroses do lead to psychoses, quotes what he describes as an old German statement "no psychoses without neurosis." There is a misunderstanding with regard to this quoted statement. It does not refer either to the neurosis or to the psychosis as a pathological condition. Indeed, the statement does not come from medicine or from psychiatry.

It originated in the field of physiological psychology. It uses the term "psychosis" to mean mental activity and the term "neurosis" to mean activity of the brain. The quotation is thus a statement of the fact that there is no mental activity without there being at the same time some activity of the central nervous system. This is a truism to us today. Such was not the case over half a century ago when the statement was first made. That was a time when psychology was essentially subjective in nature and it was necessary for the physiological psychologists forceably to remind their theoretical brethren that mental

life exists only as a corollary of neurological activities.

The use of this old statement in any other connection, particularly in relation to the pathological entities which we call neuroses and psychoses, is a total misuse of it and proves nothing whatever. It is unfortunate that these terms have, or had half a century ago, other meanings than those current in modern psychiatry.

GILBERT J. RICH, M. D.,
Roanoke, Va.

REPLY TO THE FOREGOING

Editor, THE AMERICAN JOURNAL OF PSYCHIATRY:

SIR: Dr. Rich is correct to point out my American misunderstanding of the phrase "no psychosis without neurosis." The Germans really use the statement to mean no thought without central nervous system action—a belief with which I am in agreement.

However, I misused the phrase to emphasize a second belief; namely, that in most cases a psychoneurosis preceeds the psychosis. The evidence for this belief comes from everyday clinical practice.

ROBERT ARNOT, M. D.,
Boston, Mass.

TRANSCULTURAL RESEARCH

Editor, AMERICAN JOURNAL OF PSYCHIATRY:

SIR: After considerable planning over the last several years a section on transcultural studies in psychiatry has been set up in the department of psychiatry at McGill University. The working cooperation of psychiatrists in 18 countries has been obtained and projects for joint work are being set up. The first of these was jointly set up by the department of sociology and anthropology and the department of psychiatry of McGill and was initiated this year at Lima, Peru, in association with the department of psychiatry of the Hospital Obrero under the leadership of Dr. Alberto Seguin. This project deals with the relative significance of physiological, psychological and socio-cultural factors in the etiology of the psychosomatic disorders arising from the movement of Highland Indians to coastal cities.

A second project which has been launched is the compiling of a newsletter based upon information sent in from our various coworkers in other countries. This material has been assembled and is now being sent out to psychiatrists in other countries interested in transcultural studies in psychiatry. Those interested in obtaining copies should write to Dr. E. D. Wittkower, Section on Trans-Cultural Studies, Allan Memorial Institute, 1025 Pine Avenue West, Montreal, P.Q., Canada.

EWEN CAMERON, M. D.,
Allan Memorial Institute,
Montreal, Canada

PRESIDENT'S PAGE

"The onward stream of scientific thought, although unhalting, yet so twists and eddies that the directions of its general trend may not at a given moment be plain to read."

These, the words of Sherrington, are of particular interest at this time, as we try to discern our trends and directions. Trends in psychiatry are particularly difficult to delineate because they issue so gradually from things that have gone before and because what seem to be important new developments are either not new at all or, if they are, too often miss their mark and fall by the wayside. This only can we say with any surety: Psychiatry is interlaced, as it always has been, with the prevailing concepts of man and his nature, of his place in the universe, of his purpose and his destiny, and of the forces that impinge upon him.

It was the democratic concept and the new social consciousness at the end of the eighteenth century that ushered in the great movement in the humane care of the mentally ill, associated with the name of Pinel. Today that democratic concept lives ever more strongly in our midst and social consciousness has expanded and grown until it envelops every aspect of our culture. Yet the great movement in hospital psychiatry, initiated by Pinel, has not kept pace. This is the inescapable fact of modern psychiarty, charged as it is with taking unto itself every patient whom society is unable to assimilate and, yet, all too often in no position to undertake his treatment. The distressing aspect of it is that the public has failed to identify itself with the problem and the potentialities of psychiatry cannot be fully utilized. Patients who are sick in our public mental hospitals are still required to live *en marge* of the society of which they are a part.

The shortage of staff, the dearth of researchers, nurses, and personnel in every echelon holds back our efforts to help these patients and to turn grim, outmoded, custodial institutions into therapeutic communities and centers of education, training, and research. Despite this, we are, through the dedication of our group, in a really revolutionary period in which a new social psychiatry is being written. We are certain now that much of the problem of psychiatric disability is causally related to the social environment of the patients and that the social environment in general contains precipitants in profusion for mental ill health and a wealth of perpetuating agents. It is indeed paradoxical. These patients are society's problems; they are handed to psychiatrists for treatment and cure; and, yet, that same society pays only enough for niggardly treatment and finds fault with the psychiartists because of the expense involved.

In spite of many discouraging things, however, the insights dating back to the dawn of enlightened hospital psychiatry are finding confirmation and new meaning in social and interpersonal psychiatry. Though we are in a period of change and innovation, we are mindful of the old wisdom laboriously inscribed for us by succeeding generations of students of the mind. Also, we are mindful of our unity with each other. We have, as Sherrington wrote, "an inalienable prerogative of responsibility which we cannot devolve, no not as once was thought, even upon the stars. We can share it only with each other."

FRANCIS J. BRACELAND, M. D.

COMMENT

A REPROACH TO BOTH LAW AND MEDICINE

On Sept. 17, 1955 a Denver housewife, being alone in her house, was brutally assaulted and raped, with the result that she became pregnant. She appealed to a physician to be relieved of this pregnancy. The doctor consulted the District Attorney who made public the law regarding legal abortions.

The Colorado Revised Statutes 1953, Chapter 40, Article 2, Section 23, state that a miscarriage or abortion may be induced legally *only* "with intent to save the life of such woman or to prevent serious and permanent bodily injury to her." This legal sanction was, of course, useless in the present case. The victim continued to appeal for medical help and legal protection, but in vain. Apparently no physician was courageous enough to perform an operation not specifically authorized by law, however clearly it might be indicated on humanitarian or simple common sense grounds in any civilized community.

The rapist's victim publicly expressed justified criticism of the rigidity of the law and allowed her name to be used in the newspapers in the hope that an aroused public sentiment might bring legal redress. In fact there was widespread clamor for changes in the law which would permit an abortion if the pregnancy was caused by a criminal assault.

However, nothing had been done and after 4 months her doctor told her that it was too late to perform the indicated operation safely. In due course the patient was delivered of a female child which she did not see and which was immediately placed out for adoption.

One suggestion for change in the law was to the effect that in addition to the bodily injury mentioned in the statute, the effect upon the mental condition of the victim be included in the law. This would seem to be dodging the issue or stretching a point and placing a responsibility upon the doctor that he might reasonably hesitate to assume.

The District Attorney states: "The law could be amended so that any female person who was the victim of a forcible rape, or any female child under the age of consent who was raped, resulting in pregnancy would have a right to be aborted." He adds that such a change in the law would create problems and might lead to abuse. It would seem safe to assume that any physician in good standing or any clinic to which a case such as the one here in question might be referred would make all necessary enquiries to rule out fraud. One would like to believe that the good physician, satisfying himself of the facts in the case, and without further ceremony giving his patient relief, would be quite safe from prosecution. But unhappily our society is such that one could not always be sure about that and the doctor should be given legal protection.

The statement of the District Attorney in Denver appears to cover the issue fairly and adequately, and it is to be hoped that the law in the State of Colorado may be amended accordingly. The law, so amended, would serve as a pattern for other states to follow.

LAWS

Laws are like cobwebs, which may catch small flies, but let wasps and hornets break through.

—JONATHAN SWIFT

NEWS AND NOTES

New Research Institute at New Hampshire State Hospital.—Dr. Earl K. Holt, superintendent, and Dr. G. Donald Niswander, director of psychiatic research and education, of the New Hampshire State Hospital, Concord, New Hampshire, have announced the establishment of the Arthur P. Noyes Institute for Neuropsychiatric Research. The new Institute, which was made possible by private funds under the management of the Board of Trustees of the hospital, will devote itself to the field of biochemical and physiological investigation in the problems of mental illness.

Malcolm Siegel, Ph. D., formerly associated with the Sloan-Kettering Institute for Cancer Research, and the department of biochemistry, Cornell University Medical School, has been appointed director of the newly established biochemical laboratory.

Dr. Alexander Honored.—Dr. Franz Alexander, who in 1932 founded Chicago's Institute for Psychoanalysis, the nation's first training institution for psychoanalysts, was honored at a farewell banquet on October 12, 1956, at the Blackstone Hotel, Chicago. This event marks his retirement as head of the Institute. The new director will be Dr. Gerhart Piers, himself an Institute alumnus. The principal speaker at the banquet was Dr. John Romano, chairman of the department of medicine at the University of Rochester.

Dr. Alexander gave a farewell address to the city he first came to in 1930 as visiting professor of psychoanalysis at the University of Chicago. At the end of October he moved to California to become director of the new psychiatric research center of the Mount Sinai Hospital in Los Angeles. A native of Budapest, Dr. Alexander came to Chicago from the staff of the Berlin Institute for Psychoanalysis.

Israel S. Wechsler Lecture.—The annual Israel S. Wechsler lecture will be given on the evening of December 14, 1956, at 8:30 p.m., at The Mount Sinai Hospital, New York City, by Dr. Horace W. Magoun, professor of anatomy, School of Medicine, The University of California, Los Angeles.

The subject of Dr. Magoun's lecture will be "Aristotelian Psychology and the Twentieth Century Brain."

Effects of Drugs Studied.—The Food and Drug Administration of the U. S. Department of Health, Education, and Welfare is sponsoring a pilot reporting system whereby the reactions of large groups of people to new drugs will be recorded for future clinical reference. Eleven leading hospitals are submitting reports to a central bureau, and unusual or adverse reactions to particular drugs will be carefully tabulated.

The reporting system is being developed with the collaboration of the American Association of Medical Record Librarians, the American Society of Hospital Pharmacists, the American Medical Association, and the American Hospital Association.

The First International Congress of Neurosurgery.—The First International Congress will be held in Brussels, July 21-28, 1957, in conjunction with the International Congress of Neurological Sciences.

Neurosurgeons wishing to submit papers to be read at this congress should send an abstract of 200 words to the assistant secretary-general, Dr. William B. Scoville, 85 Jefferson Srteet, Hartford, Connecticut. Registration forms which must be completed before a paper will be considered can also be obtained from Dr. Scoville. Registration fees are 15 dollars for active members, 10 dollars for associate members, and 5 dollars for members of the women's auxiliary.

The American Express Company and Thomas Cook are the official travel agencies for hotel reservations and transportation facilities for this congress.

Annual Schering Award For Medical Students.—Three increasingly important branches of medicine—cardiology, men-

tal disease, and the treatment of eye disorders—have been selected as topics for the 1957 Schering Award Contest, according to Award Chairman Dr. Chester B. Szmal.

The competition, established in 1940, is open annually to all medical students in the United States and Canada, who may submit papers on 3 topics of current medical significance.

An important new development this year is that a total of $4,500 in cash prizes will be awarded—double the amount offered in any previous year. A $1,000 first prize and a $500 second prize will be awarded for the best papers on each of the 3 selected topics.

The 3 subjects for 1957 are: (1) Incidence of Various Types of Cardiovascular Diseases by Age Group in the Male and the Female; (2) Recent Trends in Corticosteriod Therapy for Ocular Disorders; (3) Recent Advances in the Biochemical Aspects and Treatment of Mental Disease.

Students interested in participating should submit their entry forms by January 1, 1957.

American Group Psychotherapy Association.—The First Annual Training Institute of the American Group Psychotherapy Association will be held on January 9, 1957, at the Henry Hudson Hotel, New York City. On January 10, 11 and 12 the 14th Annual Conference will follow at the same location. For further information, please contact the American Group Psychotherapy Association, Room 300, 345 East 46th Street, New York City 17, by December 20, when advance registration will close.

SPECIAL NOTICE

REPORT OF THE NOMINATING COMMITTEE

The Nominating Committee announces the selection of the following candidates for election to the offices of The American Psychiatric Association for the terms beginning in May 1957:

President-Elect: Francis J. Gerty, Chicago, Ill.
Secretary: William Malamud, Boston, Mass.
Treasurer: Jack R. Ewalt, Boston, Mass.
Councilors (Three to be elected out of six nominated):
C. H. Hardin Branch, Salt Lake City, Utah
John Caldwell, Augusta, Ga.
Addison Duval, Washington, D. C.
Malcolm J. Farrell, Waverly, Mass.
Hamilton Ford, Galveston, Tex.
Jacques Gottlieb, Detroit, Mich.

Signed,

John C. Whitehorn, *Chairman,*
E. H. Crawfis
G. C. Burns
Ivan C. Berlien
Edward G. Billings

BOOK REVIEWS

Méthodes Psychométriques en Clinique: Tests Mentaux et Interpretation. By *J. Delay, P. Pichot and J. Perse.* (Paris: Masson et Cie., 1955.)

This volume, an evaluation and application of various diagnostic psychological tests, gives evidence of both wide scholarship and extensive clinical and research experience. The collaborators, two psychiatrists and a clinical psychologist, include Jean Delay, one of the outstanding contemporary French psychiatrists. Most of the procedures are well known in the United States: the Wechsler-Bellevue, the Vigotsky, the Cornell Index, the Minnesota Multiphasic, the Rosenzweig Picture-Frustration, and the Szondi test are among the tests which are carefully scrutinized. The procedures are evaluated critically from a theoretical and methodological point of view; in addition, there are a number of original studies testing the clinical validity or applicability of the procedures. The discussions are frequently stimulating. Even when the ideas are themselves not original (*e.g.*, the discussion of methods of analysis of "scatter" profiles in the Wechsler-Bellevue), the presentation is beautifully clear and incisive. The authors bring a high degree of methodological sophistication to bear on their treatment of these psychological procedures and the analysis of general issues of psychological testing is lucid and well organized. Some of the most fascinating sections deal with familiar problems in which the formulation of issues and their systematic consideration are original, *e.g.*, the rationale of a mental deterioration index, the validity of personality tests in psychiatric work, and the distinction between objective and projective tests.

Despite the merits of these critical reviews and applications of psychological tests, the discussion is limited by the basic orientation of descriptive psychiatry. There is relatively little interest in the more complex interplay of variables of dynamic psychiatry, a complexity which is both the source of richness and the core of the research difficulty. This is not to say that the authors are merely concerned with the narrow issues of making traditional diagnostic discriminations. They raise serious problems and explore some of the more difficult issues within their framework. However, their approach does not adequately explore the range of potential usefulness of psychological tests either in clinical psychiatry or in psychiatric research. For example, although the theoretical discussion of "scatter" in the Wechsler-Bellevue is excellent as far as it goes, they give scant attention to the qualitative significance of the Wechsler-Bellevue subtests and the meaning of scatter patterns, but rather focus their interest on the application of scatter analysis to the problem of mental deterioration. The authors seem well aware of the issues and problems in the psychodynamic approach to psychological testing and to clinical psychiatry and their failure to pursue these issues is unfortunate mainly because it is precisely these problems which are most in need of the kind of logical precision of thinking and research consciousness which the authors demonstrate.

The original studies in this volume involve the application of psychological tests to groups of patients and controls in order either to evaluate specific questions in psychopathology or to study the clinical value of the test. They include a range of problems such as the following: a comparison of the value of several tests in distinguishing patients with different degrees of deterioration and normal controls; a study of "latent aphasia" in patients with arterial pathology on the basis of the psychometric pattern with several test items; a study showing the value of a test of conceptual thinking (Trist-Hargreaves) in distinguishing between the conceptual ability of normals, schizophrenics, and oligophrenics; an application of the MMPI to pre- and post-ACTH and/or cortisone treatments (with a group of chronic rheumatism patients) showing that the changes in intellectual functioning subjectively experienced by patients were not mirrored in their intelligence test performances and seemed due to the affective shift from anxiety to optimism; a study of perseveration, designed to demonstrate the wide variations in the meaning of this term as used in clinical work, in the Cattell test of perseveration, and in the Rorschach; a series of studies involving the reliability of scoring of the Rosenzweig Picture-Frustration test and its applicability to studying schizophrenics; and a study of the validity of the Szondi test with negative results. These original studies are often interesting. Despite small samples, variations in adequacy of the controls, and fragmentary approaches to a diversity of problems, they are superior to the general level of clinical psychiatric research in this country. Seen as a whole, they offer no major contribution to our understanding of psychopathology, but they do present some promising leads and demonstrate the fruitfulness of psychological tests in psychiatric research.

Marc Fried, Ph. D.,
Boston Psychiatric Hospital.

Personality Changes Following Frontal Leucotomy: A Clinical and Experimental Study of the Functions of the Frontal Lobes in Man. By *P. Macdonald Tow.* (New York: Oxford University Press, 1955. Price: $8.00.)

One of the most fertile and imaginative sets of tests devised for eliciting the personality defects following frontal leucotomy is presented in this elegantly prepared small volume. The author has been working on the problem for the past ten years,

and has chosen his patients specifically on the basis that they were intellectually normal before operation. Consequently the results of leucotomy in these patients come as close as any to establishing the true effects of leucotomy uncontaminated by psychotic disturbances in thinking processes. The patients tested were chosen from a much larger number who were undergoing surgery for the relief of emotional disorders. Even of the 60 patients tested before operation only 36 were carried through the postoperative tests over a period of three full years after operation. "This reduction, which was unfortunately large, was due to some patients dying as the result of operation, or dying later; and to the fact that others, as a result of the operation, developed such symptoms that their cooperation was inadequate, or else they were not regarded retrospectively as suitable for the valid administration of tests." In other words, the examples selected for the study were among the best results obtained.

In extenuation of this attitude it is only fair to state that the author is quite aware of the recent development of limited procedures that have proven more effective and less disabling in the treatment of patients afflicted with grave psychoneuroses, and also of the restriction of major prefrontal leucotomy to "very disturbed patients. Consequently it would no longer be possible to obtain any large number of the kind of subjects studied, and, thus, there is at present no further opportunity for the experiments here presented." Here, therefore, is a study of practically normal patients subjected to extensive separation of the prefrontal areas from the rest of the brain. The picture is not a pleasing one.

Many aspects of personality function were tested before and after operation. These included intelligence (Raven's matrices), vocabulary, tempo, persistence, speed-accuracy preference, perseveration, fluency, abstract words, object-sorting, mazes, work and pleasure attitudes, "trouble questionnaire," and ink blots. Probably the most revealing of all the tests was the autobiography written by each patient before operation and long afterward. While this did not lend itself to statistical evaluation, the alteration in the attitude toward the self was very striking. It also revealed, in the patient most extensively quoted, the disastrous effect of operation: "At night, if I can manage to climb into bed, I usually wet it two or three times . . . *which* annoys me very much. Everywhere on professional grounds, I am assured that this will soon lessen into nothingness, but I myself regard this as the formation of an unbreaking habit. So what . . .?"

Decreases were particularly significant in those areas that required the display of some imagination, like the sorting of objects according to different characteristics (use, color, form, material), and decrease in vocabulary definitions and abstract words. The number of gross errors in the maze tests, and the perseveration of errors reflected the poverty of imagination displayed by the patients. Concerning the emotional reactions Tow writes: "He also has a different reaction to his own responses; he is not worried by failures; and he is not elated by successes, for he does not really seem to appreciate it. One generalization which is fairly consistently true is that his performance is considerably better in a structured situation. Where the test is completely unstructured for him as in the autobiographies, the verbal fluency tests and the abstract words, the deterioration in the performance of the frontal subject was so gross as to be obvious without quantitative comparison."

While this volume presents in detail the behavior of leucotomized patients in the test situation—and this was its single purpose—one misses the behavior of the patient when presented long after operation with the familiar routines and problems of daily life. Granted that the patients were disabled previous to operation, there is no estimate of their ability to perform their daily tasks even in spite of their enormous psychological handicaps. It comes down to the point that in the special situation of testing, these subjects were unable to perform adequately, and for the very specific reasons indicated by the author. Whether these same handicaps extended into daily life is beyond the scope of the present monograph. The author waited too long to present his material. The patients had all undergone the standard radical leucotomy before the restricted operations were coming into use. Had he been able to study patients after rostral leucotomy, orbital leucotomy, or transorbital lobotomy, the chances are that only in a few instances would he have found such enormous personality defects as those presented in his book. Nevertheless, this volume is of use in marking out the danger areas beyond which the surgeon must not trespass if he is to have a useful patient, let alone a live one. There are parts of the frontal lobe that are needlessly sacrificed in a standard prefrontal leucotomy in the plane of the coronal suture and sphenoidal ridge, particularly in patients suffering from psychoneuroses. Tow has performed a service in showing what disasters can occur when too radical surgery is performed.

WALTER FREEMAN, M. D.,
Los Altos, Calif.

AN INVENTORY OF SOCIAL AND ECONOMIC RESEARCH. Compiled by *Fred Strunk*. (Health Information Foundation 1955.)

This is the fourth publication by the Health Information Foundation of a project undertaken in 1952 aiming at listing the hypotheses, staff, geographic area covered, executing agency, financial sponsors, and publication plan of research into the social and economic aspects of health. The project is accomplished by means of a mail questionnaire distributed to a selected list or organizations and individuals. The reports are then classified, edited, and published. That the Health Information Foundation is contributing a significant service by this publication is beyond question. It gives those contemplating research some degree of continuity with the as-yet-unpublished and perhaps even incomplete efforts of their fellow workers in the field and makes for more rapid sharing of experience and

more efficient and systematic accumulation of research data.

In addition, the inventory makes available, for the first time, to all workers, rather than simply the initiated, knowledge of highly specialized reports that are rarely published. However, since the value of an inventory is in direct proportion to its completeness, it is disturbing to note, for instance, that in the first year the inventory was published only 70% of the 774 persons and organizations contacted responded to the questionnaire. And now, several years later, only 70% of the 830 persons and organizations contacted did so. It is regrettable that the Health Information Foundation did not make use of some of the well-known techniques for increasing response to mail questionnaires. Lack of response cannot automatically be equated with lack of research, since provision is made for reporting "no research." Further, an analysis of the types of organizations failing to respond leads me to suspect that some research exists among those agencies not reporting. Thus, for example, 22 of the 39 schools of public health contacted made no response at all. This is a ratio of nonresponse exceeded only by the schools of social work. In view of the active part played by these schools in research into the social and economic aspects of health—the 18 schools responding reported a total of 42 different projects—it is difficult to avoid the conclusion that unreported research projects are in progress among those not reporting. It is also difficult to understand why 35 of 81 social science research organizations failed to respond as well as 22 of 66 departments of sociology and anthropology. I also question the completeness of the original list of "contacts" when it has grown only from 774 to 830 in 3 years, and when it includes only 17 "individuals and private research organizations." One wonders how much of an additional expense it would have been to canvass the members of the appropriate professional societies and whether or not such a canvass might not at least have resulted in greater organizational response.

It would appear on the basis of the inventory that most of the research effort in the field is going into 3 areas: (1) the measurement of health levels, (2) administrative research such as need, availability, and utilization of facilities, and (3) needs, availability, utilization, and administration of personnel. More than half of the 398 research projects reported fall in the above 3 categories. By contrast, studies concerned with social and cultural data in the field of health—which one would imagine to be a dominant interest—together constitute only a fifth of the projects reported. One cannot escape the feeling that this tabulation reflects the same trend reported in so many fields; namely, the burgeoning of applied and immediate research, perhaps at the expense of more fundamental and theoretically oriented work, a trend which the Health Information Foundation itself may be interested in modifying.

Most of the studies reported by government agencies are devoted to the measurement of health levels and the need and utilization of personnel; whereas studies of social and cultural data are reported as being executed by the full range of organizations interested in health with schools of public health conducting the majority of projects.

In the reported studies, mental health plays an extremely small part. Less than 10% of the 398 studies reported are primarily concerned with problems in that field. In research in mental health, schools of medicine and governmental agencies, especially state governments, play the leading role. Only one project was reported by a school of public health or a school of social work as being primarily concerned with mental health. Of the 114 studies reported by the federal government, only 8 were concerned with mental health.

However, the small percentage of studies devoted to mental health does not give an adequate measure of the growth of the field. In 1952, when the first edition of the Inventory was published, mental health did not even appear of sufficient importance to warrant a separate indexing. Studies in mental health were scattered through the book under a variety of headings. Respondents were instructed to list all research from "1954 on and any major research completed between 1940 and 1954." In that entire publication only 16 studies were listed that could be considered as having mental health as their major focus. This can be contrasted with the almost 40 listed in the present study. Many of the 16 studies listed in the original publication were small as to finances, staff, and scope. Those listed here are almost all major enterprises with combined budgets running into many hundreds of thousands of dollars.

The area in 1952 that was "no bigger than a man's fist on the horizon" has become a major concern—the attitudes of the public toward mental illness and mental health. Several of the largest studies in 1955 are highly specialized opinion surveys devoted to exploring this area. Preliminary findings from all of the current studies, insofar as they have been informally reported at professional meetings, indicate that at completion these studies will provide, for the first time, a definitive and sharply specific baseline of popular thinking and feeling about mental illness. It is impossible to avoid the observation that there has been a general sharpening of hypotheses even in the space of 3 years. The study of the vague general social correlates to mental illness seems to have given way to the study of much more specific aspects of the interrelationship between social experience and mental illness. Accompanying this has been a general development of more rigid and quantitatively exact techniques. The "purposive sample" so frequent among the earlier studies, seems to have yielded some of its popularity to the random or probability sample. In the same way, the "free hand analysis" seems to be yielding to the rigid preformulated questionnaire or, at the very least, a carefully spelled out protocol.

In brief, there seems to have been a general refinement of the tools used in the study of the social, cultural, and economic correlates of illness. This is highly desirable, since such a refinement is the inescapable prelude to the more precise chart-

ing of what Dr. Robert Felix has termed "a whole continent of useful knowledge" that is today indicated only by the blank spaces that signify "unknown territory."

GUIDO M. CROCETTI,
New York City Community
Mental Health Board.

YEAR BOOK OF NEUROLOGY, PSYCHIATRY AND NEUROSURGERY (1955-1956 series). Edited by *Roland P. Mackay, M.D.* (Neurology), *S. Bernard Wortis, M.D.* (Psychiatry), *Percival Bailey, M.D., and Oscar Sugar, M.D.* (Neurosurgery). (Chicago: The Year Book Publishers, 1956. $7.00.)

The editor of the neurology section notes that the "outstanding neurologic event of 1955, beyond all doubt," was the production of the polio vaccine. After public release, the use of vaccine from one laboratory had been followed by attacks of poliomyelitis in 79 children, of whom 11 died and three-fourths were paralyzed. There were also 125 contact cases. After testing methods were perfected no further complications occurred, and the Salk vaccine came into use in many countries. Mackay records that in the U. S. in 1955 the vaccine "was about 75% effective in preventing paralytic poliomyelitis among those vaccinated."

He also calls attention to continuing work on the functions of the temporal lobes, their reception of a variety of sensory impulses which evoke visceral circuits and would thus appear "to offer the dynamic for extrinsic behavior." Further, "the temporal lobes, and in particular their inferior and medial portions become indispensable to memory, but not its sole repository."

Many valuable contributions to our knowledge of the degenerative diseases are also cited. Further studies of the convulsive disorders emphasize "that EEG patterns are not readily translatable into clinical terms . . . The current easy appeal to the EEG for the answer to all questions of diagnosis, prognosis and therapy is more than ever to be deprecated."

In introducing the psychiatric section Wortis notes that the present period in psychiatric history is likely to be remembered as the era of psychopharmacology. While warning against the panacea obsession, he conservatively records that the newer drugs "are often remarkably helpful in the treatment of some neurotic and psychotic reactions."

Intensive work is being carried on in the field of experimental psychiatry. The production of psychosis-like reactions by injections of lysergic acid and related substances and their resolution by the use of other drugs.

"Advances . . . in the physical and pharmacologic therapies have done much to move psychiatry closer to medicine in its broadest and best application, and have also shown that the psychiatrist needs to be a physician with many skills, biologic, psychologic and social."

Wortis foresees the advent of "newer and better anxiety- and tension-relieving drugs," the performance of "fewer total lobotomies," and more effective treatment by "newer electric and ultrasonic procedures."

Bailey and Sugar, in their introduction to the section on neurosurgery, devote most of their remarks to severe criticism of the operation of lobotomy in the treatment of mental illness. They quote with approval the assaults on this procedure by the Belgian, J. Ley. They seem to accept this author's concession that there is only one justification for lobotomy—the relief of violent suffering, either moral or physical. They recall with emphasis the Hippocratic maxim: *primum non nocere.*

They note that with the use of the newer drugs "the temptation to use it [lobotomy] early in the course of a mental illness has been practically eliminated."

Among other neurosurgical procedures the editors refer to temporal lobectomy introduced by Bailey and Gibbs for psychomotor epilepsy. These authors' warnings against *bilateral* invasion of the medial part of the temporal lobe has not always been heeded—with disastrous results.

Since Cushing opened the door to brain surgery, ever wider and deeper areas of that organ have been made accessible to remedial tchniques or exposed to experimental interference. Bailey and Sugar sum it up: "By all means let us continue to search for new methods of alleviation of human ailments, but always mindful of our responsibilities as physicians."

C. B. F.

EFFECTS OF ALCOHOL ON THE NERVOUS SYSTEM OF MAN. By *Cyril B. Courville, M.D.* (Los Angeles: San Lucas Press, 1955. $4.50.)

It is of importance that Dr. Courville, with his tremendous experience as a neuropathologist, has written this volume dealing with the underlying patholgy of the many and varied neurological and psychotic syndromes found in alcoholics. As he says in his epitome, "with the exception of the direct effect of alcohol on the stomach and indirectly on the liver, the chief action of alcohol is exerted on the brain, spinal cord and peripheral nerves."

He discusses in successive chapters the pathology of (1) acute alcoholic intoxication and delirium tremens, (2) Wernicke's encephalopathy, (3) peripheral neuropathy, (4) alcoholic cerebral cortical atropy, (5) chronic alcoholic psychoses (Korsakoff's Psychosis, alcoholic pellagra and chronic alcoholic deterioration), (6) post-alcoholic commissural and central necrosis (Marchiafava-Bignami Disease), (7) alcoholic cerebellar degeneration, and (8) spinal cord degenerations incident to chronic alcoholism.

While he postulates a direct toxic action of alcohol on the nervous parenchyma producing histiotoxic changes somewhat similar to those seen in anoxia, he stresses the importance of accompanying vitamin deficiency in chronic alcoholic syndromes.

The book is fully illustrated and there is a useful bibliography. The proof reading has been poor, re-

sulting in statements confusing to the reader, *e.g.* on page 87.

Eric A. Linell, M. D.,
Toronto, Canada.

Alcoholism—Its Psychology and Cure. By *Frederick B. Rea.* (New York: Philosophical Library, 1956. $3.50.)

This little book is intended for popular reading and is slanted toward the religious approach to the problem of alcoholism. The final chapter is labeled, "The Spiritual Causes of Addiction," and states, "Addiction, therefore, is more than a personality disorder; it is a character disorder. It is not simply a psychological disease; it is a spiritual disease, a malady of the soul. . . . We are also enabled to understand why something more than a medical or psychological cure is needed for such cases. Spiritual diseases demand spiritual remedies." The book ends with a plea that the Christian Church should unite with public welfare services and the medical profession to abolish alcoholism.

The book is divided into 3 parts: Part One, of 4 chapters, related to addiction; Part Two, also 4 chapters, discusses cure; and Part Three, the conclusions, labeled, The Spiritual Causes of Addiction. The author starts out with a discussion of the complexity of the problem of alcoholism, in which he seems largely to accept the attitude of psychiatry. Chapter 2, on the metabolism of alcohol, is, on the whole, a fair presentation of the subject for popular reading. A few minor errors creep in which are not particularly important. Chapter 3 discusses what types tend to become alcoholics. This is, again, a rather good, common sense discussion. There is particular emphasis on the fact that Jews are less likely to become alcoholics, although they show a higher percentage of occasional drinkers and a lower percentage of abstainers than do Protestants or Catholics. The author sees the importance of a cultural attitude here and feels that we should learn something from the approach of the Jewish culture. Chapter 4, "The Road to Alcoholism," discusses the manner in which individuals go on to become alcoholics.

Part Two discusses cure. The author accepts the attitude of Alcoholics Anonymous that alcoholism cannot be cured, it can only be arrested. He likewise accepts the general medical idea that those who have been alcoholics cannot be restored to normal habits of moderate drinking. The first chapter in Part Two discusses the different aversion treatments, and he finds the conditioned reflex treatment unsatisfactory; the use of apomorphine as comparable to shock therapy of contemporary psychiatry; the antabuse treatment as having some value but not yet used enough to know all of its possibilities. Medical hypnosis he seems to regard as having important potentialities. Chapter 6 is a discussion of the significance of conversion, which is in accord with the commonly accepted views of what takes place in religious conversion. Chapter 7 is a discussion of Alcoholics Anonymous, and Chapter 8 is entitled "The Pastor and the Alcoholic."

After its preliminary discussion of alcoholism from other standpoints this small book concentrates on the religious approach. From this standpoint it is slightly different from a number of other popular books that have been written on the subject. On the whole, the material on alcoholism is suitably presented for popular reading.

K. M. B.

Reactions with Drug Therapy. By *Harry L. Alexander.* (Philadelphia and London: W. B. Saunders Company, 1955.)

This volume is a boon to pharmacologists and clinicians who are at loss to deal with the unusual experiences that at times accompany drug therapy. A book with this scope should be welcomed in the library of the clinician and of a hospital. The practicing dentist will find the chapters on sedative, anti-infectious, and local anaesthetic drugs very useful. It is comforting to learn that the potential capacity to induce sensitization is limited to certain drugs and that hypersensitive reactions to drugs fall, as a rule, into well-defined common patterns. An excellent list of references is included in the book.

G. H. W. Lucas, M. D.,
University of Toronto.

Handbook of Parliamentary Procedure. By *Henry A. Davidson, M. D.* (New York: The Ronald Press Co., 1955. Price: $3.75.)

Your reviewer had the privilege of commenting upon Dr. Davidson's *Forensic Psychiatry* in these columns and of hearing his lucid exposition of forensic issues on various occasions. He has a solid and well-deserved reputation as a writer and speaker in the field of forensic psychiatry.

Readers who have come to expect something better than average from this author will not be disappointed in his latest book. The contents are described in the beginning of the preface: "This handbook aims to present in simple step-by-step terms the rules and practices of parliamentary procedure for the small organization. . . ."

The contents include such matters as rules of procedure; work of committees, boards and commissions; construction of a constitution; the structure of a budget and examples of forms in common use.

Reading of the section on "precedence of motions" would save many a chairman from embarrassment and audiences from the annoyance arising out of bumbling and incompetent direction of a meeting.

Dr. Davidson's treatise fills an urgent need and should receive a wide and favorable response.

K. G. Gray, M. D.,
University of Toronto, Canada.

IN MEMORIAM

ESTHER LORING RICHARDS, M. D.

1885–1956

Dr. Esther Loring Richards died at the age of seventy-one on July 6, 1956, at her home in Baltimore. Her church, The Franklin Street Presbyterian, was crowded for the memorial service with friends from every walk of life, for her missionary efforts in behalf of psychiatry had extended to every segment of the Baltimore community, and her varied interests had made her a member of many formal and informal groups in the city.

Dr. Richards graduated from Mount Holyoke College, took her first year in medicine at the University of Wisconsin, and transferred then to the Johns Hopkins Medical School, from which she was graduated in 1915. She immediately entered the newly established Henry Phipps Psychiatric Clinic as an intern, and remained associated with the Phipps Clinic until her death. She was in charge of the outpatient service of the Clinic from 1920 until her retirement in 1951, and was associate professor of psychiatry in the University from 1923. Her service therefore spanned twenty of the thirty years of Adolf Meyer's regime, and ten years of that of John C. Whitehorn.

She taught a whole generation of medical students, and her forceful, clear, and pungent case presentations emphasizing the practical devices for measuring behavior—"the tests of life"—will not soon be forgotten by those students. She was a prodigious worker, and managed always to extract some fun even from the most arduous effort. She was an excellent speaker, much in demand the country over. She was honored as "Woman of the Year" in science in 1946.

She was the author of two books: *Behavior Aspects of Child Conduct* (1932), and *Introduction to Psychobiology and Psychiatry* (1941), besides a full hundred articles. She held the honorary degree D. Sc. from Mount Holyoke, Wilson, and Goucher Colleges.

She was the trusted consultant for numerous organizations in the city including The Baltimore City Hospitals, various family care organizations, the schools, and, among others, Catholic, Protestant and Jewish charitable organizations. She was on the original Medical Advisory Board of The Seton Institute.

Of Welsh descent, her great love was music, and for long years she was a sponsor of and attendant at The Bach Festival in Bethlehem, Pa. In her last months of semi-invalidism, she was much cheered by the visits of her friend, Mme. Agi Jambor, who played the piano for her.

She had unbelievable courage in the face of the long illness which she knew would bring death, and she carried on an extensive practice from her wheel chair until the last two weeks.

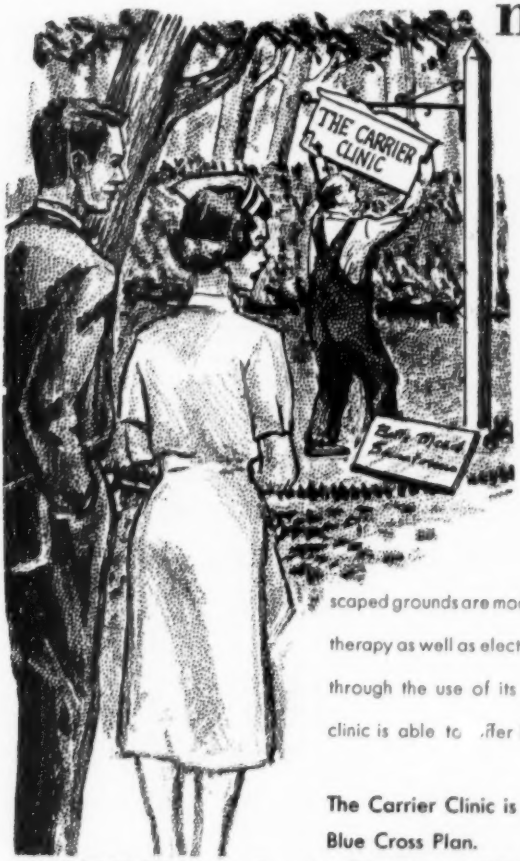
Burial was in South Yarmouth, Massachusetts.

RUTH E. FAIRBANK, M. D.
WENDELL MUNCIE, M. D.

Esther Loring Richards

1885–1956

A new *sign* in the search for mental health



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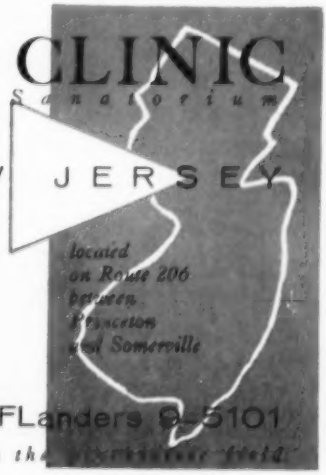

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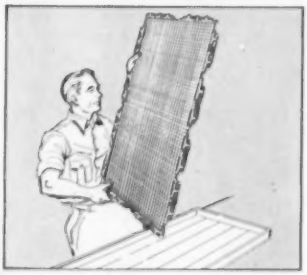
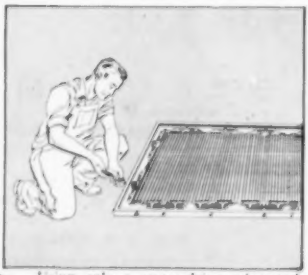


2 Replacement screen panel with all hardware applied in proper position is shipped by express.

3 When replacement arrives a hospital maintenance man simply removes hinge pins and lays swing section of unit on the floor.



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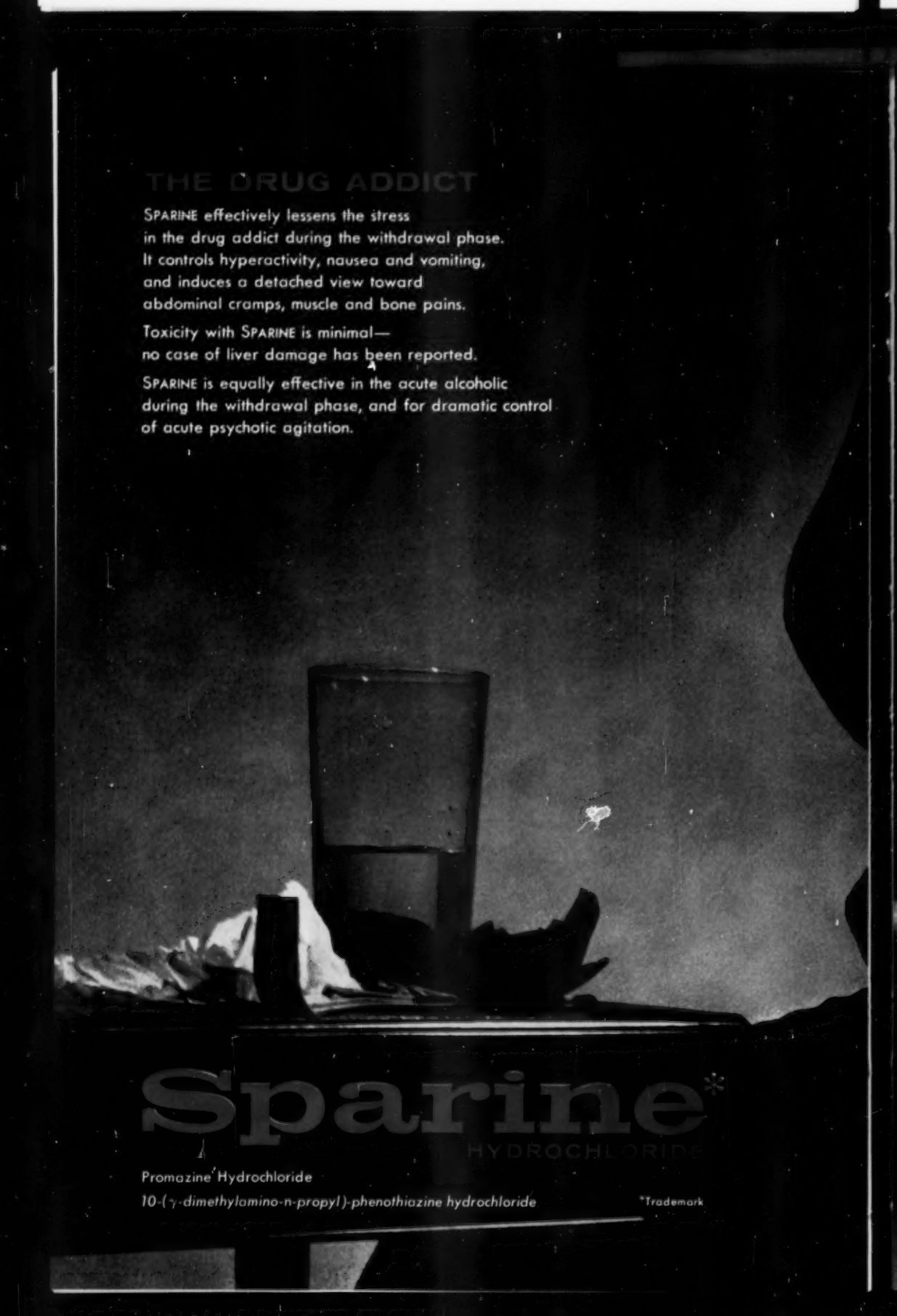
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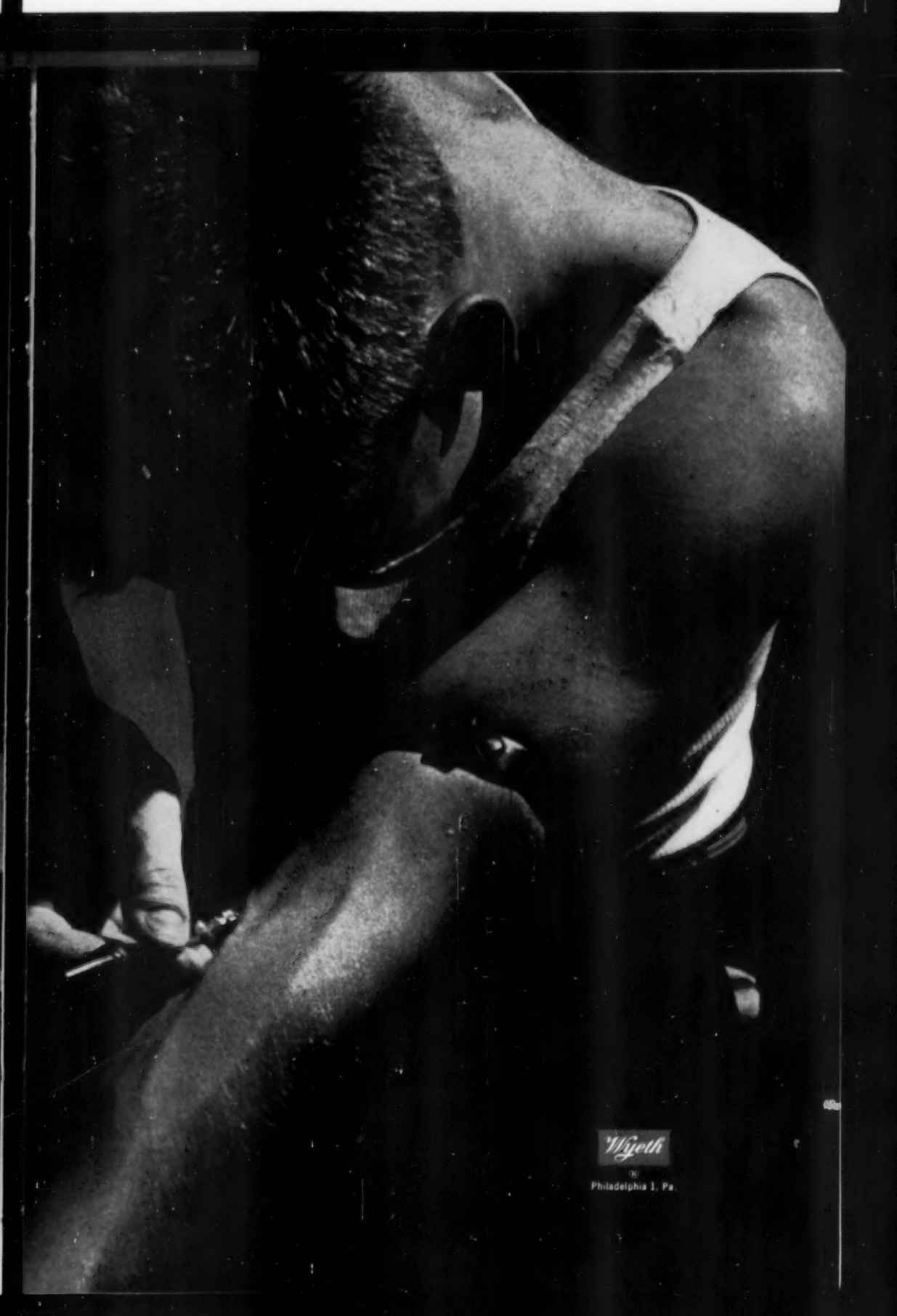
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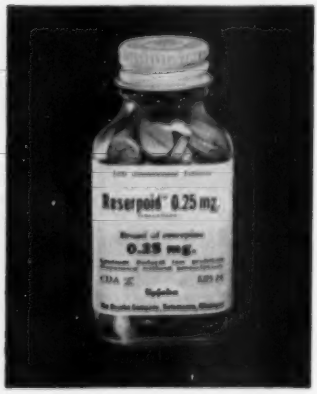

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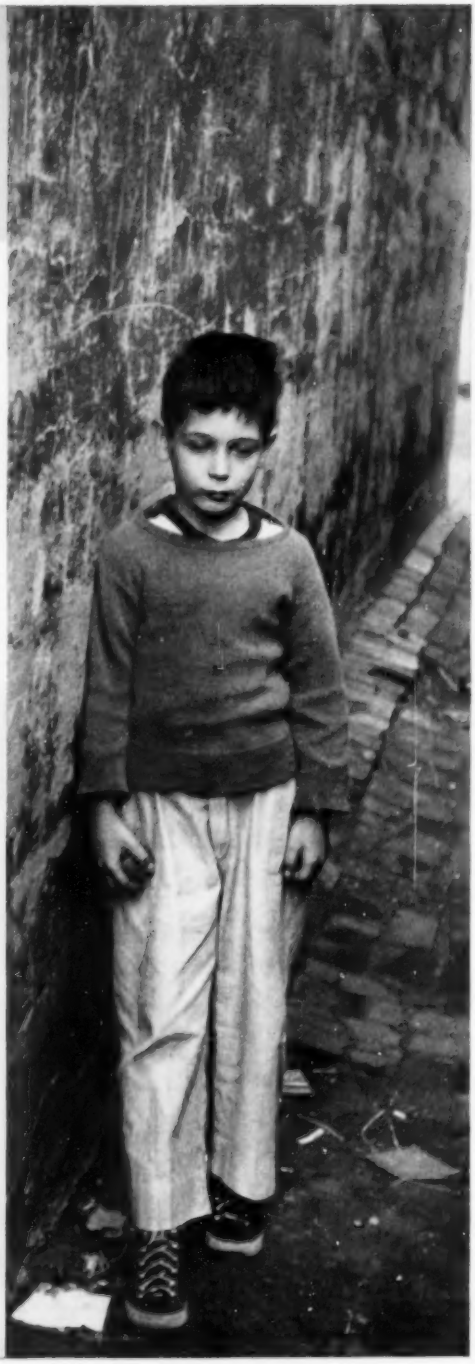

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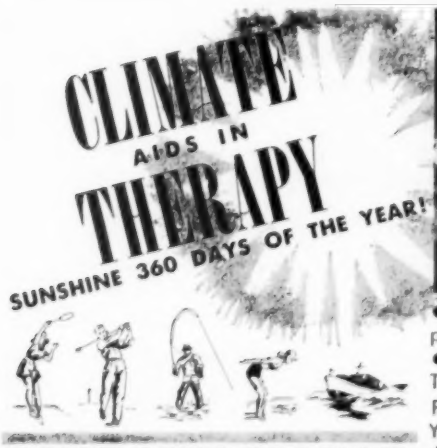

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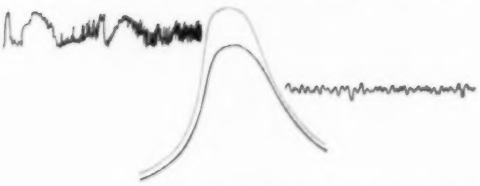

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1. Doyle, P. J., and Livingston, S.: J. Pediat. *43*:413 (Oct.) 1953.
2. Livingston, S., and Petersen, D.: To be published.
3. Pence, L. M.: Texas State J. Med. *50*:290 (May) 1954.

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